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Proposed Registration Document PRD2014-10

Cyflumetofen

(publié aussi en français)

31 March 2014

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2014-10E (print version)
H113-9/2014-10E-PDF (PDF version)

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Overview

Proposed Registration Decision for Cyflumetofen

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Cyflumetofen Technical and Nealta Miticide, containing the technical grade active ingredient cyflumetofen, to control European red mite and twospotted spider mite and McDaniel spider mite on pome fruits, grape, strawberry, and tomato.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Cyflumetofen Technical and Nealta Miticide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on cyflumetofen, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on cyflumetofen, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation section of this consultation document.

What Is Cyflumetofen?

Cyflumetofen is a compound in the benzoylacetonitrile class of chemistry. It interferes with energy production within cells and acts as an acaricide on contact with spider mites. Foliar application of cyflumetofen formulated as Nealta Miticide provides control of European red mite, twospotted spider mite and McDaniel spider mite on pome fruits, grapes, strawberries and tomatoes.

Health Considerations

Can Approved Uses of Cyflumetofen Affect Human Health?

Nealta Miticide, containing cyflumetofen, is unlikely to affect your health when used according to label directions.

Potential exposure to cyflumetofen may occur through diet (food and water), when handling and applying the product, or when entering an area that has been treated with the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used, according to label directions.

In laboratory animals, the technical grade active ingredient cyflumetofen was of low acute toxicity by oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and non-irritating to the skin. Cyflumetofen did cause an allergic skin reaction; consequently, the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product, Nealta Miticide, was low via the oral, dermal and inhalation routes of exposure. Nealta Miticide was non-irritating to the eyes, minimally irritating to the skin, and did not cause an allergic skin reaction.

Cyflumetofen did not damage genetic material. There was evidence of testicular tumours and thyroid tumours in the rat; however, the endpoints selected for risk assessment are considered protective of these findings. There was no indication that cyflumetofen caused damage to the nervous system or immune system. Cyflumetofen did not cause effects on the ability to reproduce. Health effects in animals given repeated doses of cyflumetofen included effects on the adrenal glands, liver, kidneys, ovaries and testes.

When cyflumetofen was given to pregnant rabbits, a marginal shift in the normal pattern of bone growth was observed in fetuses at a dose which produced body weight and liver weight changes in the mothers. At the highest dose level, malformations of the paws were observed in fetuses; additional effects in the mothers included decreased food consumption and adrenal gland effects. When cyflumetofen was administered to pregnant or nursing rats, effects on the developing fetus (delayed bone ossification) and juvenile animal (slight delays in sexual maturation, adrenal gland effects) were observed at doses that were also toxic to the mothers, as evidenced by toxicity to the adrenal glands. These results indicate that the young do not appear to be more sensitive to cyflumetofen than the adult animal.

The risk assessment protects against the effects of cyflumetofen by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 1-2 years of age — the subpopulation which would ingest the most cyflumetofen relative to body weight — are expected to be exposed to less than 6.3% of the Acceptable Daily Intake (ADI). Based on these estimates, the chronic dietary risk from cyflumetofen is not of concern for all population subgroups. Cyflumetofen is not carcinogenic, therefore a cancer dietary exposure assessment is not required.

The deterministic acute aggregate dietary intake estimate for females 13-49 years of age from exposure to cyflumetofen is 0.75% of the Acute Reference Dose (ARfD). A single dose of cyflumetofen is not likely to cause acute health effects to any other population subgroup.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established Maximum Residue Limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States of American using cyflumetofen on Citrus Fruits (CG 10-revised), Pome Fruits (CG 11-09), Tree Nuts (CG 14-11), grapes, strawberries, and tomatoes were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Risks in Residential and Other Non-Occupational Environments.

Potential residential exposure and risk for the general public (adults, youths and children) entering Nealta Miticide treated fields to pick their own fruit are considered acceptable.

Occupational Risks From Handling Nealta Miticide

Occupational risks are not of concern when Nealta Miticide is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply as well as field workers who re-enter freshly treated fields can come in direct contact with Nealta Miticide residues on the skin. It is specified on the label that anyone mixing, loading Nealta Miticide and doing clean-up and repairs must wear a long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks, and that anyone applying the product must wear a long-sleeved shirt, pants and shoes plus socks. In addition, wear a suitable dust mask approved by NIOSH/MSHA when handling. The label also specifies that workers do not enter treated fields for 12 hours after application. Taking into consideration these label requirements, health risks to agricultural workers are not of concern.

For bystanders, exposure is expected to be much less than that of field workers and can be considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens when Cyflumetofen is Introduced into the Environment?

Cyflumetofen is not persistent in terrestrial and aquatic environments. At the proposed use rates, cyflumetofen and its transformation products present a negligible risk to the majority of terrestrial and aquatic non-target organisms. However, a risk was identified for non-target terrestrial plants and amphibians.

Cyflumetofen enters the environment when used as an insecticide against mites on various crops. Cyflumetofen is not persistent in the terrestrial environment where biotransformation and hydrolysis in moist soils are the main routes of transformation. Cyflumetofen is not expected to volatilize, and leaching to groundwater is not a concern.

Cyflumetofen is not persistent in the aquatic environment. Once in water, it rapidly undergoes transformation by photolysis and hydrolysis at environmentally relevant pHs, and particularly alkaline pH. Cyflumetofen is also rapidly broken down by microbial activity in water and sediments, and it is not expected to bioaccumulate in fish tissue.

Many transformation products of cyflumetofen were identified in the abiotic transformation laboratory studies, and in the soil and aquatic biotransformation laboratory studies. Most major transformation products were further investigated. Generally, major transformation products having a large chemical structure similar to cyflumetofen, such as AB-1 and AB-1 dimers, tend to be immobile like the parent; while those with a small chemical structure (having a single benzene ring only), such as A-2, B-1 and B-3, tend to be mobile in soil.

Cyflumetofen can be applied by field sprayer or air-blast sprayer (late and early season). Non-target terrestrial and aquatic habitats may be exposed to the chemical as a result of spray drift or runoff. At the proposed use rates, cyflumetofen presents a negligible risk to terrestrial organisms such as earthworms, beneficial insects (bees and other beneficial arthropods), birds and small mammals. However, a risk to non-target terrestrial plants was identified. Cyflumetofen is not expected to pose a risk to freshwater or marine fish, invertebrates, or algae, but a risk was identified to amphibians. To minimize the risk resulting from off-field drift to sensitive non-target organisms, spray buffer zones will be required between the treated area and sensitive terrestrial and aquatic habitats downwind of the treatment area. No environmental risks were identified from exposure to the major transformation products of cyflumetofen.

Value Considerations

What Is the Value of Nealta Miticide?

Nealta Miticide provides control of European red mite, twospotted spider mite and McDaniel spider mite on pome fruits, grapes, strawberries and tomatoes.

Nealta Miticide is applied using ground-based application equipment to the foliage of listed orchard, vineyard and field crops to control spider mites. It is effective against all life stages of spider mites and provides residual control. There are no other Group 25 acaricides registered in Canada, giving cyflumetofen particular value for resistance management.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Nealta Miticide to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

As users may come in direct contact with Nealta Miticide on the skin or through inhalation of spray mists, anyone mixing and loading Nealta Miticide and during clean-up and repairs, must wear a long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks. Applicators must wear a long-sleeved shirt, long pants and shoes plus socks. In addition, they are required to wear a suitable dust mask approved by NIOSH/MSHA when handling Nealta Miticide. The label also specifies that workers not enter treated fields for 12 hours after application. Moreover, a standard label statement to protect against spray drift to unintended areas during application is on the label. Taking into consideration these label statements, the number of applications, and the duration of exposure for workers, the health risks to these individuals are not of concern.

Environment

To reduce the exposure of terrestrial and aquatic habitats to cyflumetofen, the PMRA is proposing further risk reduction measures which include:

- A hazard statement to inform the user that this product is toxic to non-target terrestrial plants and aquatic organisms;
- Guidance to reduce runoff from treated areas into aquatic areas; and
- Spray buffer zones of up to 5 metres are required to protect sensitive terrestrial habitats, and up to 3 metres are required to protect sensitive aquatic habitats.

Next Steps

Before making a final registration decision on cyflumetofen, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision, and the Agency's response to these comments.

Other Information

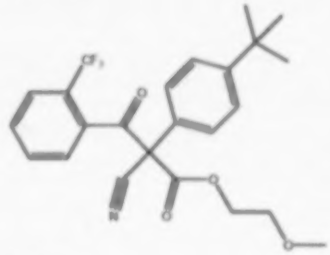
When the PMRA makes its registration decision, it will publish a Registration Decision on cyflumetofen (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Cyflumetofen

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Cyflumetofen
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2-methoxyethyl (*RS*)-2-(4-*tert*-butylphenyl)-2-cyano-3-oxo-3-(α,α,α-trifluoro-*o*-tolyl)propionate
2. Chemical Abstracts Service (CAS)	2-methoxyethyl α-cyano-α-[4-(1,1-dimethylethyl)phenyl]-β-oxo-2-(trifluoromethyl) benzenepropanoate
CAS number	400882-07-7
Molecular formula	$C_{24}H_{24}F_3NO_4$
Molecular weight	447.45
Structural formula	
Purity of the active ingredient	98.6%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product - Cyflumetofen Technical

Property	Result
Colour and physical state	Pale yellow powder
Odour	Odourless
Melting range	77.9-81.7ºC
Boiling point or range	269.2ºC at 2.2kPa
Density	1.299 g/cm³ at 20ºC

Property	Result
Vapour pressure at 25°C	$< 5.9 \times 10^{-6}$ Pa
Henry's law constant at 20°C	$<9.227 \times 10^{-7}$ atm·m³/mol
Ultraviolet (UV)-visible spectrum	pH λ_{max} ε (L·mol^{-1}·cm^{-1}) 0.91 199 37153.52 7.34 199 36307.81 13.33^{a} 291 19952.62 256 11748.98 $^{a)}$ The UV/VIS absorption spectrum obtained from the basic test solution was believed to contain the spectrum of decomposed product of the test substance.
Solubility in water at 20°C	28 µg/L at pH 7
Solubility in organic solvents at 20°C (g/L)	Solvent — Solubility *n*-hexane — 5.16 methanol — 98.7 toluene — > 500 dichloromethane — > 500 acetone — > 500 ethyl acetate — > 500
n-Octanol-water partition coefficient (K_{OW})	Log K_{ow} = 4.3 at 25°C
Dissociation constant (pK_a)	-4.19 (estimated using the Perrin calculation method)
Stability (temperature, metal)	Stable up to 293°C

End-Use Product - Nealta Miticide

Property	Result
Colour	Milky white
Odour	Odourless
Physical state	Liquid suspension
Formulation type	Suspension (SU)
Guarantee	200 g/L
Container material and description	High density polyethylene (HDPE) jugs and totes (0.40-1000 L)
Density	1.0682 g/cm³ at 20°C
pH of 1% dispersion in water	6.42 at 25°C
Oxidizing or reducing action	Product does not react with water, oxidizing agents (potassium permanganate), reducing agents (iron) and it is not hazardous when in contact with fire extinguishing agents like monoammonium phosphate

Property	Result
Storage stability	Stable for one year when stored under warehouse conditions in fluorinated HDPE containers; stable for 12 weeks at 54°C
Corrosion characteristics	No physical changes in the HDPE containers when stored under warehouse conditions for one year
Explodability	Product is not explosive

1.3 Directions for Use

Crop(s)	Pest(s)	Amount of product per application (L/ha)	Pre-Harvest Interval (days)
Grape	European red mite Twospotted spider mite McDaniel spider mite	1	14
Pome Fruits (Crop Group 11-09) Apple Asian pear Azarole Crabapple Japanese quince Mayhaw Medlar Pear Quince	European red mite Twospotted spider mite McDaniel spider mite	1	7
Strawberry	Twospotted spider mite McDaniel spider mite	1	1
Tomato	Twospotted spider mite	1	3

[1] Maximum of 2 applications per growing season.

[2] Allow a minimum of 14 days between applications. Monitor pest population and reapply if necessary once thresholds are reached.

[3] Apply in a minimum spray volume of 500 L/ha. Higher water volumes are recommended for thorough coverage.

[4] Do not apply if rain is expected within one hour.

[5] Ground application only. Do not apply by air.

[6] Do not apply through any type of irrigation system.

[7] Do not use in the greenhouse.

1.4 Mode of Action

Cyflumetofen is a mitochondrial complex II electron transport inhibitor (Mode of Action Group 25) and thus, interferes with cellular energy metabolism. It acts through direct contact with the target pests and has no systemic activity in plants but is active against all life stages of spider mites (Tetranychidae), including eggs.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Cyflumetofen Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) and high-performance liquid chromatography methods with UV detection were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media.

In plant and animal commodities, LC-MS/MS methods were developed and proposed for data gathering and enforcement. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal commodities.

Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Cyflumetofen Technical (hereinafter referred to as cyflumetofen) is a member of the acrylonitrile class of compounds with a novel mode of action – mitochondria complex II electron transport inhibition. Cyflumetofen exerts its miticidal activity by disrupting steroid metabolism, leading to lipid accumulation in various tissues.

A detailed review of the toxicological database for cyflumetofen was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Limited studies (acute oral and/or mutagenicity battery) were also conducted with metabolite B-1 (major rat and plant metabolite), metabolite B-3 (major environmental degradate with potential for human exposure through drinking water), and a substance that is an impurity (AB-13) from the formulation process of the Technical Grade Active Ingredient (TGAI). The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to cyflumetofen.

In acute toxicity testing, cyflumetofen was demonstrated to be of low toxicity via the oral, dermal and inhalation routes in rats. Cyflumetofen was minimally irritating to eyes and non-irritating to the skin of rabbits. It is considered to be a dermal sensitizer based on results from a maximization test in guinea pigs.

The end-use product, Nealta Miticide, was demonstrated to be of low acute toxicity via the oral, dermal and inhalation routes of exposure in rats. It was non-irritating to the eyes, minimally irritating to the skin of rabbits and not a dermal sensitizer based on results from a local lymph node assay conducted in mice.

^{14}C-radiolabelled cyflumetofen, radiolabeled at the butylphenyl (A-ring) or tolyl (B-ring) position, was rapidly absorbed following gavage administration of a single oral high dose in rats. The maximum plasma concentration was reached at approximately one to four hours post-dosing, and 35-46% of the administered dose was absorbed. Following administration of a single low dose, greater absorption (68-78%) was observed, with maximum plasma concentrations reached at approximately one hour post-dosing. Plasma concentrations were not dose-related, indicating that absorption was saturated at the high dose. In addition, a comparison of the results following single and repeated low-dose administration indicated the potential for saturation of absorption with repeated low-dose administration. No significant differences in absorption were observed between sexes. The removal of cyflumetofen from plasma occurred rapidly and followed biphasic first-order kinetics.

Cyflumetofen was widely distributed among tissues and organs, with the highest levels of radioactivity detected in portal of entry and primary excretion tissues (for example, the gastrointestinal tract, liver and kidney), as well as the carcass. By 72 hours post-dosing, less than 2.5% of the administered dose (AD) remained in the body. Overall, the toxicokinetics data for cyflumetofen did not suggest a potential for bioaccumulation.

In the elimination balance study, excretion of cyflumetofen occurred primarily via the urine (58-67% AD for the low-dose and 14-26% AD for the high-dose groups) and feces (25-33% AD for the low-dose and 68-80% AD for the high-dose groups). In the biliary excretion study, the amount of radioactivity eliminated in urine was lower than that determined in the elimination balance study at the same sampling time, suggesting that a portion of the administered radioactivity excreted via the bile (24-37% AD for the low-dose and 18-32% AD for the high-dose groups) was re-absorbed from the intestinal tract via enterohepatic recirculation.

The data indicated that cyflumetofen is metabolised, primarily via hydrolytic cleavage of the trifluorotolyl group (B-ring moiety), resulting in metabolite B-1, the primary metabolite in rats and plants. The parent compound was not identified in urine; however, it was found in feces at varying levels (2-4% low-dose and 54-66% high-dose) following administration of both radiolabels.

In a limited plasma kinetics study in the mouse, cyflumetofen, radiolabelled at the tolyl ring, was rapidly absorbed following single oral dose administration at various dose levels. The maximum plasma concentration was observed at 0.5 to one hour post-dosing, with females showing a second T_{max} at two or eight hours post-dosing, depending on the dose level. Plasma concentrations declined rapidly after reaching peak concentrations, with females exhibiting higher internal doses than males.

The adrenal glands were the primary target organ of toxicity in mice, rats and dogs. Following repeat dietary dosing in mice (28-day, 90-day and 18-month), the only effects noted were on the adrenal glands and included cortical cell vacuolation and hypertrophy, as well as changes in adrenal weight and size. In the short-term dietary toxicity studies conducted in rats (14-day, 28-day and 90-day), the primary target organ was also the adrenal glands. Like the mouse, rats demonstrated evidence of adrenal toxicity including vacuolation and hypertrophy of adrenal cortical cells, and changes in adrenal weight, size and colour. Similar adrenal findings were also observed in rats in the 90-day dietary neurotoxicity study and the 28-day dietary immunotoxicity study. Rats exhibited additional toxicity to the liver (increased organ weights, clinical chemistry changes and histopathology findings), kidneys (increased organ weights, clinical chemistry changes), and ovaries (vacuolation of interstitial gland cells and corpora lutea, increased weight). Body weight gain, food consumption and food efficiency were affected in rats only at the limit dose of 1000 mg/kg bw/day. Following longer-term dosing in the rat, toxicity to the testis (atrophy of seminal vesicles and coagulating gland) was also observed. The results of the rat chronic toxicity and oncogenicity studies identified effect levels for adrenal toxicity similar to those of the short-term studies for both mice and rats.

Twelve-month, 90-day and 28-day oral (via capsule) toxicity studies in the dog were available. The main findings in these studies consisted of adrenal effects similar to those observed in rats and mice; increased adrenal weights and vacuolation of adrenal cortical cells were noted at the lower doses, with incidence and severity increasing with dose. Decreased body weight gain, food efficiency (males only), food consumption (females only), and triglycerides were noted at the limit dose of 1000 mg/kg bw/day. In addition, adrenal cortical cell degeneration, adrenal interstitial cell fibrosis, lymphocyte infiltration of the adrenals, increased size of the adrenals and swelling of the interstitial cells of the testes were observed in the 12-month study in dogs.

In a well-conducted 28-day dermal toxicity study in the rat, increased kidney and liver weights were noted, although they were without histopathological correlates.

A comparison of the results of repeat dose studies among the three species tested indicated that the rat was the most sensitive species, with females appearing to be slightly more sensitive to the adrenal effects following exposure to cyflumetofen than males. While rats and mice did not appear to be affected by the duration of dosing, this was not the case in dogs, where the incidence and severity of effects on the adrenal glands increased following longer exposures.

In a developmental toxicity study in rats, there was no evidence of sensitivity of the young. There was a marginal, but treatment-related increase in the fetal incidence of incomplete ossification of sternal centra that was observed at the same dose producing increased adrenal gland weights and adrenal gland cortical cell vacuolation in dams. An increased incidence of wavy ribs was seen in fetuses at the highest dose level (limit dose of testing). In the rabbit developmental toxicity study, a marginal shift in skeletal ossification pattern was observed in fetuses at the mid-dose level, a dose level producing increased liver weights in the dams. At the highest dose level (limit dose of testing), dams exhibited decreased body weight gain and food consumption. Decreases in fetal weight and placental weight as well as changes to hyoid alae, fused or incompletely ossified sternal centra, and an increased number of ossified caudal vertebrae were recorded. Further, at this dose level, a serious endpoint (malformation of the fore/hind paws) was observed in fetuses at the same dose producing maternal toxicity (decreased body weight gain and food consumption).

Reproductive toxicity was investigated in a dietary range-finding and 2-generation study in the rat. In the range-finding study, effects were limited to the adrenal glands and consisted of adrenal cortical cell vacuolation and hypertrophy. In the 2-generation study, adrenal effects were observed in both parents and offspring (F_1 and F_2 progeny) at the mid-dose and included an increase in adrenal weight and adrenal cortical cell hypertrophy. At the high dose, a decrease in pre-mating body weight gain was noted in parental females, while a decrease in body weight during lactation was noted in F_2 offspring. There was also a slight delay in sexual maturation in female offspring (F_1, mid and high dose) and in male offspring (F_1, high dose). In terms of effects defining the reproductive toxicity No Observed Adverse Effect Level (NOAEL), effects were observed in high-dose animals only and included decreased estradiol, Follicle Stimulating Hormone (FSH), and progesterone, a marginal increase in estrous cycle length, vacuolation of ovarian interstitial cells (F_1 females) and increased ovary weights (P_0). There were no effects on any of the reproductive indices. There was no evidence of sensitivity of the young in this study.

In addition to the reproductive toxicity studies, a battery of *in vitro* endocrine screening studies was provided. In a steroidogenesis assay using H295R cells, cyflumetofen increased estradiol concentrations at ≥ 5 µM and decreased testosterone concentrations at ≥ 1 µM. Assays including aromatase (human recombinant), estrogen receptor transcriptional activation (HeLa-9903 cells), estrogen receptor (rat uterine cytosol) and androgen receptor (rat prostate cytosol) binding indicated that cyflumetofen was negative for inhibition of CYP19 aromatase activity and estrogen transcriptional activation, non-interactive with the estrogen receptor, and a non-binder with the androgen receptor. The overall evidence for potential reproductive toxicity did not reveal any effects on reproductive performance or outcome.

A standard genotoxicity battery, consisting of an Ames test, chromosome aberration, mammalian gene mutation and Unscheduled DNA Synthesis (UDS) assays, was available for the technical active ingredient. The results of these tests indicated that cyflumetofen was not genotoxic.

The requirement for chronic toxicity/oncogenicity testing was addressed through submission of an 18-month mouse oncogenicity study, a one-year rat chronic toxicity study and a 2-year rat oncogenicity study. In addition, the applicant elected to conduct confirmatory studies for each one. Each of these confirmatory studies had a control group as well as one treatment group that received the test material at a dose that was higher than the highest dose of each of the respective original studies. The PMRA was informed that these studies were conducted in order to address any residual uncertainty regarding the animals being adequately challenged in the original studies. The confirmatory studies were conducted at the same laboratory, using the same strain of animals and under the same testing conditions as those employed in the original studies; however, the studies were conducted 10 years apart.

With regards to the mouse, there was no evidence of oncogenicity at the highest dose level in the original study (approximately 500 mg/kg bw/day) or in the confirmatory study (approximately 1140 mg/kg bw/day); the only findings at the latter dose were effects on the adrenal gland (vacuolation, deposition of brown pigment and increased weight) and spleen (enlargement and extramedullary hematopoiesis).

In the original one-year rat study, effects on the adrenal glands included vacuolation and hypertrophy of the cortical cells and increased weights. In addition, males exhibited atrophy of the seminal vesicles and coagulating glands while females exhibited increased ovary weights and vacuolation of the ovarian interstitial gland cells. In the confirmatory one-year rat study, in which rats received doses of cyflumetofen that were approximately four times higher than those administered in the original studies, adrenal effects similar to those observed in the original chronic study were noted, as well as effects in the ovaries. These effects on the ovary occurred at a dose where the animals were displaying signs of stress, as evidenced by decreased bodyweight and body weight gain relative to control animals. In addition, males exhibited focal atrophy of the acinar cells of the pancreas, a common spontaneous degenerative lesion in the Fischer rat, and hyperplasia of the interstitial cells in the testes. Testicular interstitial cell hyperplasia, which is a common finding in aging Fischer rats, was only observed at the one-year terminal sacrifice and not at any of the earlier scheduled interim sacrifices.

Results of the original rat oncogenicity study indicated no evidence of treatment-related tumours; however, it was recognized that the animals could have tolerated higher doses. In the confirmatory two-year rat oncogenicity study, a statistically significant increased incidence of testicular interstitial cell (Leydig cell) tumours was observed in male rats (96% in treated animals vs. 76% in controls). It was postulated by the applicant that cyflumetofen creates transient decreases in serum testosterone, resulting in increased serum luteinizing hormone (LH) levels, which in turn, leads to Leydig cell hyperplasia and proliferation to tumours. The induction of Leydig cell tumours by this Mode of Action (MOA) is generally regarded to exhibit a threshold, and is largely considered of low relevance to humans. Leydig cell tumours are common age-related lesions in Fischer 344 rats (background incidence of 75-100%) as reflected in the incidence of these tumours in the study controls (76%). While there was limited information to support the proposed MOA, overall concern for the increased incidence of Leydig cell tumours was low, in large part due to the high background rate of the concurrent controls in the confirmatory study.

In this same study, there was also an increased incidence of thyroid tumours in treated males. The non-statistically significant incidence of thyroid c-cell carcinomas (30%) as well as the statistically significant combined incidence of thyroid c-cell adenomas and carcinomas (57%) was increased over that of the study controls (18% and 38%, respectively). The incidence of carcinomas in concurrent controls was at the upper limit of reported historical control values (18%) while the incidence of combined thyroid tumours was slightly above that of recent historical control values (50%), which have been increasing in recent years. A proposed mode of action for these tumours was not submitted by the applicant. Although two carcinogenicity studies in the rat, conducted under the same conditions, were available, there were challenges in using the combined results from these studies to aid in the interpretation of carcinogenic potential. The studies were conducted approximately 10 years apart. The historical control data covering the timespan of the two studies indicated that the background rate of thyroid tumours has been increasing, which was mirrored by differences in the concurrent control values for both studies. These differences resulted in limitations in being able to combine the study results to characterize the thyroid tumour dose response; consequently, a quantitative linear low dose extrapolation could not be performed. In considering the overall information, however, it was noted that there was no increase in the incidence of non-neoplastic thyroid pathology in either the original or confirmatory study. In addition, the mortality rate was not affected by tumour development; the thyroid tumours were observed in animals that died very late in the study or were sacrificed at study termination.

In consideration of the above information for the Leydig cell tumours and thyroid c-cell tumours, as well as the fact that the genotoxicity battery was negative and there was no evidence of oncogenicity in the mouse, it was determined that a threshold approach was necessary for the cancer risk assessment due to limitations in the available data as outlined above.

In an acute neurotoxicity study conducted via gavage in rats, no clinical signs of toxicity, effects on motor activity, or adverse histopathology were noted. Similarly, in a 90-day dietary neurotoxicity study, no evidence of neurotoxicity was noted in rats; however, adrenal effects (vacuolation and increased weights) were noted in both sexes.

A 28-day dietary immunotoxicity study was conducted on rats using the ELISA method to measure serum immunoglobulin M (IgM) responses following immunization with sheep red blood cells (SRBC). There was no evidence of an immunotoxic response; however, adrenal effects (increased size and weight, change in colour, vacuolation) were observed at the mid- and/or high-dose levels in both sexes.

Acute oral toxicity studies for the major plant and rat metabolite B-1, as well as for impurity AB-13 revealed low acute toxicity via the oral route in rats. Clinical findings of toxicity from the in vivo UDS test appear to indicate that metabolite B-3 is more acutely toxic than cyflumetofen via the oral route. Genotoxicity studies were available for metabolites B-1 and B-3 and impurity AB-13. A genotoxicity screening battery consisting of an Ames test, chromosome aberration, mammalian gene mutation and UDS assays was conducted using metabolites B-1 and B-3. The gene mutation assay was found to be positive for both metabolites, in the absence of metabolic activation, following prolonged exposure (24 hour treatment) only. The remaining studies were found to be negative, with the exception of the Ames test for metabolite B-3, which indicated a positive response in the absence of activation for Salmonella strain TA100 only. For impurity AB-13, the genotoxicity battery consisted of an Ames test, and mammalian gene mutation and chromosome aberration assays. All results were negative for impurity AB-13.

Structural activity relationship analyses were conducted on metabolites B-1 and B-3 and impurity AB-13 using DEREK. DEREK is a computer program that performs a structural activity analysis by comparing the query structure to a knowledge base of toxicophores (fragments of structures with biological activity) for which there is toxicological information. DEREK was used to assess several aspects of toxicity including carcinogenicity, genotoxicity, developmental toxicity and teratogenicity, irritation, skin sensitization and thyroid toxicity.

DEREK analyses indicated no structural alerts for metabolite B-1 or B-3. DEREK analysis of AB-13 predicted that this impurity might cause α-2-μ-globulin nephropathy in rats. Kidney effects that result from this neuropathy are sex- and species-specific and are not considered to be a hazard to human health. Developmental and testicular toxicity was also predicted for AB-13 due to the presence of the monomethyl glycol ether moiety that can be released from the ester function. As this moiety is also present in the chemical structure of the parent compound cyflumetofen, the effect of this moiety has been assessed in the toxicity testing performed with cyflumetofen.

Results of the toxicology studies conducted on laboratory animals with cyflumetofen and its associated end-use product are summarized in Appendix I, Tables 2 and 3. Results from toxicity studies conducted with metabolites or impurity of cyflumetofen are summarized in Appendix I, Tables 4 and 5. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. As of 15 April 2013, three incident reports involving cyflumetofen have been submitted to the PMRA. The incidents in question are scientific studies (steroidogenesis, confirmatory one-year rat study and select information from the confirmatory two-year rat carcinogenicity study) discussed previously in this consultation document.

3.1.1 Pest Control Products Act Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for cyflumetofen. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the 2-generation reproductive toxicity study. Marginal delays in sexual maturation in female offspring as well as adrenal gland effects (weight changes, hypertrophy) were observed at doses that produced the same adrenal effects in parental animals. In a developmental toxicity study in rats, an increased incidence of incomplete ossification of sternal centra was observed in fetuses in the presence of maternal toxicity (for example, sadrenal affects). An increased incidence of wavy ribs was noted in fetuses at the highest dose level (limit dose of testing). In the rabbit developmental toxicity study, a marginal shift in skeletal ossification pattern was observed in fetuses at the mid-dose level, a dose producing increased liver weights in the dams. At the highest dose level (limit dose of testing), a serious endpoint (malformation of the fore/hind paws) was observed in fetuses in the presence of maternal toxicity (decreased body weight gain and food consumption).

Overall, the database is adequate for determining the sensitivity of the young. There is a low concern for sensitivity of the young and effects on the young are well-characterized. The fetal malformations observed in the rabbit developmental toxicity study were considered serious endpoints although the concern was tempered by the presence of maternal toxicity. Therefore, the *Pest Control Products Act* factor was reduced to three-fold for scenarios in which the endpoint of malformations from the rabbit developmental toxicity study was used to establish the point of departure for assessing risk to women of reproductive age. For exposure scenarios involving other sub-populations, including children, the risk was considered well-characterized and the *Pest Control Products Act* factor was reduced to one-fold.

3.2 Determination of Acute Reference Dose

Females 13-49 Years of Age

For females 13 to 49 years of age, the most appropriate endpoint to estimate acute dietary risk to cyflumetofen was from the rabbit developmental toxicity study. A NOAEL of 250 mg/kg bw/day, based on malformations observed at 1000 mg/kg bw/day, was selected for risk assessment. These effects were considered possibly to result from a single exposure and are therefore relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 3-fold when using the endpoint of malformations from the rabbit developmental toxicity study to establish the point of departure for assessing risk to women of reproductive age. The Composite Assessment Factor (CAF) is 300.

The ARfD (for females 13 to 49 years of age) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{250\ \text{mg/kg bw/day}}{300} = 0.8\ \text{mg/kg bw of cyflumetofen}$$

General Population (excluding females 13-49 years of age)

An acute reference dose is not required for the general population (excluding females 13-49 years of age) as a relevant endpoint of concern was not identified in the database.

3.3 Determination of Acceptable Daily Intake (ADI)

To estimate risk from repeated dietary exposure, the two-year dietary rat oncogenicity study with a NOAEL of 16.5 mg/kg bw/day was selected for risk assessment. The Lowest Observed Adverse Effect Level (LOAEL) for this study was 49.5 mg/kg bw/day, based on adrenal toxicity and uterine effects. Although the 2-generation reproduction study in the rat identified a lower NOAEL (9.2 mg/kg bw/day, based on adrenal toxicity and marginal delays in sexual maturation at the LOAEL of 30.6 mg/kg bw/day), this is believed to be the result of dose spacing and dose level selection when a comparison of the NOAELs and LOAELs of these repeated-dose studies is undertaken. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to one-fold. The composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{16.5 \text{ mg/kg bw/day}}{100} = 0.2 \text{ mg/kg bw/day of cyflumetofen}$$

This ADI provides a margin of approximately 1250 to the NOAEL for malformations in the fetuses of female rabbits and a margin of approximately 1100 to the dose where a treatment-related increase in tumours was observed in the confirmatory rat oncogenicity study.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term Dermal Risk Assessment

For short-term dermal risk assessment for adults, the developmental toxicity study in rabbits was selected. The rat 28-day dermal toxicity study did not address the serious endpoint of concern from the rabbit developmental toxicity study, and when dermal absorption (11%) is considered, would not provide the necessary protection to this endpoint. For these reasons, use of the rabbit developmental toxicity study was selected for risk assessment. At the highest dose level of 1000 mg/kg bw/day, malformations were observed in the presence of maternal toxicity. A NOAEL of 250 mg/kg bw/day was established.

For residential scenarios (residential exposure resulting from commercial application), the target Margin of Exposure (MOE) selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As outlined in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to three-fold. This MOE is considered to be protective of all subpopulations, including the unborn children of exposed women.

For occupational scenarios, the target MOE for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability. As the worker population could include pregnant women, it is necessary to afford adequate protection of the fetus which may be exposed via its mother. In light of concerns regarding prenatal toxicity as outlined in the *Pest Control Products Act* Hazard Characterization section, an additional three-fold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13-49 years of age.

Intermediate- and Long-term Dermal; Inhalation (all durations)

For these scenarios, the NOAELs of 16.5 mg/kg bw/day from the 90-day oral rat and two-year rat dietary oncogenicity studies were selected for risk assessment. Toxicity was observed in these studies in the form of adrenal effects in both sexes. The use of the 28-day dermal study was not considered for the intermediate and long-term dermal scenarios as there was evidence of durational effects in the dog studies, and the dermal study did not assess an endpoint of concern in the database (for example, malformations in the rabbit developmental toxicity study). With regards to the selection of inhalation endpoints for risk assessment, a repeat-dose inhalation study was not available and thus, use of a NOAEL from an oral study was appropriate. For these reasons, the NOAEL of 16.5 mg/kg bw/day from the aforementioned oral studies was selected and provided protection to the malformations.

The target MOE for these scenarios is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of this study and MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Acute Aggregate (females 13-49 years of age)

Acute aggregate exposure to cyflumetofen may be comprised of food, drinking water and oral and dermal exposure from harvesting activity at pick-your-own farm operations. Toxicological endpoints and assessment factors are the same as those for the acute reference dose for females 13-49 years of age (see section entitled Acute Reference Dose).

Acute Aggregate (general population — excluding females 13-49 years of age)

An acute aggregate assessment is not required for the general population (excluding females 13-49 years of age) as a relevant endpoint of concern was not identified in the database.

Cancer Assessment

On the strength of the overall information, it was determined that a threshold approach was necessary for cancer risk assessment for the observed thyroid c-cell tumours and Leydig cell tumours in male rats due to the limitations in the available data. Overall, the endpoints selected for non-cancer risk assessment are considered to be protective of these findings.

3.4.1.1 Dermal Absorption

Rat *in vivo* and human in vitro studies were submitted to determine the dermal absorption for Nealta Miticide. No rat in vitro study was submitted; therefore, the North American Free Trade Agreement (NAFTA) triple pack approach was not considered further. The human in vitro study was considered as supplemental information.

A dermal absorption value of 11% for cyflumetofen was determined from the rat in vivo study where a single dermal application of radiolabelled cyflumetofen was made at three dose levels (2, 20 and 2000 μg/cm^2) in groups of rats. These dermal doses were selected based on the application rate of the concentrated and diluted spray product expected in fields in actual use conditions. The majority of the administered dose was recovered in first skin wash after 8-hours of exposure at all dose levels (85-95%). Recovery of the applied radioactive dose (mass balance) was acceptable at all doses levels (93-108%). The dermal absorption, as a percent of applied radioactive dose, increased over the monitoring period of five days at all dose levels, but decreased with increase in dose. The dermal absorption, for example, the total amount of cyflumetofen absorbed over time by each animal, as the sum of the quantity found in the excreta, blood, carcass and skin was highest (11%) in the low dose group of rats.

3.4.2 Occupational Exposure and Risk

Occupational exposure to Nealta Miticide is characterized as short- to intermediate-term for farmers and custom applicators that mix, load, and apply, and are predominantly by the dermal and inhalation routes. Postapplication exposures for re-entry workers are expected to be short- to intermediate-term, and occur primarily by the dermal route. Acute Pick-Your-Own (PYO) residential exposure may occur by the dermal and dietary routes of exposure.

3.4.2.1 Mixer/Loader/Applicator Exposure and Risk Assessment

Farmers and custom applicators have potential for dermal and inhalation exposures during mixing, loading and applying Nealta Miticide on grape, pome fruit, tomato and strawberry crops. These exposures are expected to be of short- to intermediate-term in duration. Chemical-specific passive dosimetry exposure data for Mixer, Loader and Applicator (M/L/A) were not submitted. Therefore, the M/L/A exposures were generated using the generic unit exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. The exposure estimates are based on mixers and loaders wearing a single layer of clothing (long pants and long-sleeved shirt) plus gloves and applicators wearing a single layer of clothing and no gloves.

The dermal exposures were estimated by coupling the generic PHED M/L/A unit exposures with the amount of active handled per day calculated based on default area treated per day for each crop and the efficacy supported single application rate of 200 g a.i./ha for all crops. The 11% dermal absorption value was used in the assessment. Inhalation exposure was estimated by coupling the generic PHED inhalation unit exposures with the amount of active handled per day and 100% inhalation absorption. The daily M/L/A exposure estimates were normalized to mg/kg bw/day using 80 kg adult body weight.

MOEs were calculated by comparing the toxicology endpoints selected for the expected occupational scenarios, with the estimated short- and intermediate-term dermal and inhalation exposures. The target MOE is 300 for short-term and 100 for intermediate-term exposures. The estimated MOEs for farmers and custom applicators mixing, loading and applying Nealta Miticide, exceed the target MOEs and are not of concern. The dermal and inhalation exposure and risk estimates are presented in Appendix I, Table 6.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

3.4.2.2.1 Grape Dislodgeable Foliar Residue study

Chemical specific grape Dislodgeable Foliar Residue (DFR) study was designed to establish a DFR dissipation curve for Cyflumetofen 20 SC (BAS 9210-0I) following two foliar applications at 13-15 days interval to grape vines, at three sites in the United States of America: Pennsylvania, California, and Oregon. At each site, Cyflumetofen 20 SC, a soluble concentrate formulation with an adjuvant was applied at 200 g a.i./ha/application with air blast sprayer equipment. Triplicate DFR samples were collected before and after the first and second application and at several intervals up to 35 days after the last application. Additional samples from the untreated control plot were collected and fortified with known concentrations of cyflumetofen to determine the field recovery of cyflumetofen residues. As field recovery was less than acceptable (≤95%) at each site for lower and/or higher level of fortifications, field sample results were corrected (where applicable) for incomplete recovery. The DFR data from each site were fitted with linear regression analysis. The average peak DFR after the second application was ≤13.4% at each site and linearly declined to ≤3% at the end of sampling period of 35 days. The half-life of cyflumetofen on grape leaves was estimated as 14 days at the Pennsylvania site, seven days at the California site and 23 days at the Oregon site.

Geographical and climatic conditions were relevant to Canadian growing regions of Southern Ontario, southern British Columbia and southern Quebec. The DFR value from the Pennsylvania site, with the highest average peak residue (0.268 μg/cm^2) following linear dissipation and an R^2 value of >0.85, was used in deriving postapplication exposure estimates for Canadian re-entry workers entering cyflumetofen treated grape fields.

3.4.2.2.2 Postapplication Exposure and Risk Estimates

Agricultural workers who may enter treated crop fields to conduct various postapplication activities have potential for exposure mainly by the dermal route. Inhalation exposure potential is low based on the low vapour pressure of cyflumetofen ($<5.9 \times 10^{-9}$ kPa at 25°C), which qualifies for NAFTA inhalation waiver of $<1 \times 10^{-4}$ kPa at 20-30°C for outdoor use. In addition, Nealta Miticide formulation contains 70% water and will be further spray diluted in at least 500 L of water before application. Thus, the inhalation exposure potential is negligible and further assessment is not required.

The postapplication dermal exposures were estimated by coupling the DFR from the chemical specific DFR study for grapes and default DFR values for all other crops, with the highest activity specific Transfer Coefficients (TCs) for each crop, 11% dermal absorption, default body weight (80 kg) and 8 hours duration of work per day. MOEs for each activity were calculated for both, the short- and the intermediate-term durations, as separate toxicology end points were provided for these dermal exposures. The postapplication exposure and risk estimates for Nealta Miticide, on the day of second application, are presented in Appendix I, Table 7. As the MOEs for highest exposure activity for each crop exceed the target MOEs, the exposure and risks for all crop maintenance activities occurring after the first and/or second application of Nealta Miticide are not of concern. Therefore, only a default Restricted-Entry Interval (REI) of 12 hours is required to allow for residues to dry.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Handler Exposure and Risk

There are no domestic class products; therefore, no residential handler risk assessment is required.

3.4.3.2 Postapplication Exposure and Risk

There is potential for postapplication exposure to the general population entering treated orchards, strawberry fields, or coming in contact with residential fruit trees treated with Nealta Miticide.

3.4.3.2.1 Acute Aggregate Exposure Assessment for Pick-Your-Own Fruit

Potential acute residential exposure may occur for the general public (adults, youths, and children) entering Nealta Miticide treated apple, pear and strawberry fields to pick their own fruit. Therefore, there is potential for PYO acute dermal exposure while picking fruit, and acute dietary exposure while eating the picked fruit on the same day for adults (18+), youth (10-12), and children (1-9). As the acute toxicology reference dose was identified only for one subpopulation, females of 13-49 years of age, the aggregated PYO exposure and risk is estimated only for this subpopulation and is acceptable. For all other subpopulations, the acute dermal and acute dietary PYO exposures are not of concern.

The PYO dermal exposures for apple, pear and strawberries were estimated based on the maximum application rate of 200 g a.i./ha, default DFR of 0.6144 $\mu g/cm^2$ after two applications, TC of 1400 cm^2/hour for hand harvesting apples and pears, and TC of 1100 for hand harvesting strawberries, the exposure duration of 2 hours during picking activities and 11% dermal absorption value.

For the PYO acute dietary exposures, the Dietary Exposure Evaluation Model (DEEM) consumption data for apple, pear and strawberries in grams of commodities consumed/day (95%), and maximum residue of cyflumetofen detected in fields from the crop field trials for cyflumetofen were used. Based on these data, the acute dietary exposures in mg /kg bw/day for apples, pears and strawberries for females of 13-49 years of age were calculated.

The acute aggregated exposure was estimated by summing the calculated acute dermal and the acute dietary exposures. The acute aggregate risk was estimated based on the acute aggregate end point of 250 mg/kg bw/day for females of 13-49 years of age. The aggregated acute exposure and risk estimates are presented in Appendix I, Table 8.

For pome fruit and strawberries, the PYO aggregate exposure and risk for a subpopulation of toxicological concern (females of 13-49 years of age) are acceptable on the day of second application where the potential for exposure is highest considering the Pre-Harvest Interval (PHI) is seven days for pome fruit and one day for strawberries.

3.4.3.2.2 Residential Fruit Trees

This commercial product could potentially be used on residential/private fruit trees. Children are not expected to engage in activities associated with the treated trees. Dermal exposures to adults and youths through contact with transferable residues are represented by hand harvesting and are expected to be short- to intermediate-term in duration. However, these exposures are expected to be significantly less than the postapplication occupational exposures and not of concern. There is no appropriate aggregation endpoint for dermal exposures and chronic dietary exposures except for the females, 13-49 years of age group, which is considered to be the most at-risk subpopulation. The exposure for females 13-49 years of age from this scenario is expected to be below the exposure from the PYO scenario considering the shorter exposure time of 0.67 hours.

3.4.3.3 Bystander Exposure and Risk

The product will be handled mainly by workers, and application is limited to agricultural crops under conditions to minimize the spray drift to areas of human habitation. Therefore, bystander exposure and risk are expected to be less than that of field workers and, therefore, are not of concern.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products is cyflumetofen and in animal commodities is cyflumetofen and metabolite B-1. The data gathering/enforcement analytical methods are valid for the quantitation of cyflumetofen residues in citrus crops (CG 10-revised); pome fruits (CG 11-09); tree nuts (CG 14-11); small fruit vine climbing subgroup, except fuzzy kiwi fruit (CSG 13-07F); low growing berry subgroup (CSG 13-07G); and tomatoes and for the quantitation of cyflumetofen and the B-1 metabolite in livestock commodities. The residues of cyflumetofen are stable in various crops when stored in a freezer at <-10°C for ~25 months with some exceptions where residues were stable for ~11 months. Some corrections to residues were thus required to account for losses due to frozen storage. Raw agricultural commodities were processed, and residues in processed commodities were analyzed.

Processing factors were determined, and the majority of edible processed commodities showed a reduction in residues upon processing. However, for citrus peel and oil, apple sauce, and raisins, cyflumetofen residues concentrated (1.4-119×). Quantifiable residues are not expected in ruminant commodities when exposed to treated feed. Supervised residue trials conducted throughout the representative NAFTA growing regions using end-use products containing cyflumetofen at the approved rates in or on various crops are sufficient to support the proposed MRLs.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.16), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994-1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following assumptions were made in the basic chronic analysis: 100% crop treated, default processing factors and residues of cyflumetofen in/on citrus crops (CG 10-revised); pome fruits (CG 11-09); tree nuts (CG 14-11); small fruit vine climbing subgroup, except fuzzy kiwi fruit (CSG 13-07F); low growing berry subgroup (CSG 13-07G); and tomatoes at the proposed MRL levels. Residues in ruminant commodities that may have been exposed to treated feed were based on the limit of quantitation (LOQ) values. The basic chronic dietary exposure from all supported cyflumetofen food uses (alone) for the total population, including infants and children, and all representative population subgroups are <6.1% of the ADI. Chronic aggregate exposure to cyflumetofen residues from food and water is considered acceptable for the total population (1.6% (0.0027 mg/kg bw/day) of the ADI) and children 1-2 years, the highest exposed subgroup, (6.3% (0.0108 mg/kg bw/day) of the ADI).

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were made in the basic acute analysis: 100% crop treated, default processing factors and residues of cyflumetofen in/on citrus crops (CG 10-revised); pome fruits (CG 11-09); tree nuts (CG 14-11); small fruit vine climbing subgroup, except fuzzy kiwi fruit (CSG 13-07F); low growing berry subgroup (CSG 13-07G); and tomatoes at the proposed MRL levels. Furthermore, residues in/on ruminant commodities were based on LOQ values. The basic acute dietary exposure (food alone) for all supported cyflumetofen-treated commodities is estimated to be 0.71% (0.0059 mg/kg/day) of the ARfD for females 13-49 years old (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable: 0.75% of the ARfD for females 13-49 years old.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for cyflumetofen consists of exposure from food and drinking water sources only, there are no residential uses. Aggregate risks were calculated based on acute (females 13-

49 years old) and chronic endpoints. There was no acute endpoint identified for the general population, including infants and children.

3.5.4 Maximum Residue Limits (MRL)

Table 3.5.4.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Citrus oil	16.0
Small fruit vine climbing subgroup, except fuzzy kiwi fruit (Crop subgroup 13-07F); low growing berry subgroup (Crop subgroup 13-07G), apple sauce	0.6
Citrus peel and tomatoes	0.4
Citrus fruit (Crop Group 10-revised); Pome fruit (Crop Group 11-09)	0.3
Tree nuts (Crop Group 14-11)	0.01
Fat, meat and meat byproducts of cattle, goats, horses, and sheep	0.03
Milk	0.003

For additional information on MRL in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in animal and plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 9 and 10.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties, cyflumetofen is sparingly soluble in water and is not likely to volatilize from moist soil or water surfaces under field conditions. The log octanol/water partitioning coefficient for cyflumetofen suggests the potential for bioaccumulation in the food chain. However, the mean steady-state bioconcentration factor for whole fish indicates a low potential for cyflumetofen and its transformation products to bioaccumulate in fish and living organisms (see Section 1.2 of this consultation document).

When cyflumetofen enters the terrestrial environment, it is expected to sorb to soil. Cyflumetofen is non-persistent in aerobic soil, where it undergoes microbial biotransformation. Under anaerobic (flooded) soil conditions, cyflumetofen was also found to be non-persistent. Photolysis is not expected to contribute to the transformation of cyflumetofen on soil, while hydrolysis can occur in moist soils and the rate increases with increasing pH.

Although the use pattern for cyflumetofen does not include direct application to water, the possibility that aquatic systems will be exposed to cyflumetofen and its major transformation products, directly or indirectly, cannot be ruled out. Once in the water, cyflumetofen is expected to rapidly hydrolyse, especially in alkaline environments. Phototransformation can also contribute to the dissipation of cyflumetofen from the water layer in the photic zone. Cyflumetofen was found to be non-persistent in both aerobic and anaerobic water/sediment systems.

Through biotic and abiotic processes in soil and in water, cyflumetofen transforms into several transformation products. Some of the most important major transformation products, A-2, B-1, B-3, AB-1, and AB-1 dimer, were further tested to determine their fate and behaviour in the environment.

B-1 was found in every biotic and abiotic transformation pathway from both terrestrial and aquatic systems, being slightly more persistent than the parent compound. B-3 was a major transformation product detected in soil from microbial biotransformation, predominantly in aerobic systems, and was non-persistent to slightly persistent. AB-1 is unstable in soil, being readily transformed to AB-1 dimers. Further transformation of the several transformation products of cyflumetofen will result in the formation of trifluoroacetic acid (TFA) and carbon dioxide (CO_2). Trifluoroacetic acid is a common transformation product of pesticides.

Laboratory studies on adsorption/desorption indicate that cyflumetofen, AB-1 and AB-1 dimer are immobile in soil, A-2 has a low- to moderate-mobility, while B-1 and B-3 have the potential to be very highly mobile in soil. In a terrestrial field study conducted with cyflumetofen in an eco-region relevant to Canada, the parent and B-1 were found to dissipate quickly, which supports the laboratory results indicating they will be non-persistent in the environment, with no evidence of leaching in the soil column below a 15-cm soil depth; other transformation products were either not detected or sparingly detected over time. Furthermore, the observation of B-1 as the primary field degradation product is consistent with the aerobic soil laboratory experiments.

Based on the leaching criteria of the ground water ubiquity score, which considers persistence (aerobic soil biotransformation half-lives) and organic-carbon partition coefficients (Koc), low solubility in water, and a terrestrial field study showing little movement below 15 cm, cyflumetofen is not considered to be a potential leacher.

Based on adsorption/desorption data, minimal mobility is expected for AB-1, AB-1 dimer and A-2 in soil. Based on the groundwater ubiquity score, both B-1 and B-3 are considered as potential leachers. But as no significant vertical movement of these transformation products was detected in the terrestrial field dissipation study, leaching in soil into groundwater of these two compounds, under typical use and soil conditions, is also expected to be minimal. Overall, cyflumetofen and its transformation products are not expected to reach groundwater.

The list of all major transformation products of cyflumetofen is presented in Appendix I, Table 11; data on the environmental fate and behaviour of cyflumetofen and several major transformation products are summarized in Appendix I, Table 12.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated Environmental Concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (for example, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. Screening level EECs for cyflumetofen on plant surfaces, on soil and in soil (15-cm incorporation) are presented in Appendix I, Table 13 and concentrations in vegetation and insect food sources for birds and mammals are presented in Appendix I, Table 14.

A Risk Quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the Level of Concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible. Refined EECs for cyflumetofen spray drift input to water are in Appendix I, Table 15 and for cyflumetofen runoff input to water are in Appendix I, Tables 16 and 17. Refined EECs for cyflumetofen spray drift off-field on non-target plants are in Appendix I, Table 21.

4.2.1 Risks to Terrestrial Organisms

Cyflumetofen enters the terrestrial environment when used as a field or an airblast application on strawberry, tomato, grapes, or pome fruit. Non-target terrestrial organisms may be exposed to cyflumetofen through direct application, contact with treated material, or from ingestion of contaminated food.

A risk assessment of cyflumetofen, its end-use product Nealta Miticide, and the transformation products B-1 and AB-1 was undertaken for terrestrial organisms based on available toxicity data for each of the compounds. A summary of terrestrial toxicity data is presented in Appendix I, Table 18 and the accompanying screening level and refined risk assessments are in Appendix I, Tables 19 to 21.

The screening level RQs for cyflumetofen were based on the seasonal maximum application rate of Nealta Miticide (two applications of 200 g a.i./ha, at a 14-day interval), and either a soil DT_{50} value of 4.56 days (as the 90th percentile confidence bound on the mean of eight, n=8, representative half-life values adjusted to 25°C obtained in the aerobic soil biotransformation studies), or a default foliar half-life of 10 days. Under these conditions, the maximum terrestrial cumulative application rate for soil is 223.8 g a.i./ha per year, and for plants is 275.8 g a.i./ha per year. The EECs for the transformation products B-1 (n=5) and AB-1 (n=3) were also calculated using this method, resulting in soil half-life values of 18.54 days and 18.18 days, respectively.

Earthworms: Cyflumetofen, its end-use products and the major transformation products B-1 and AB-1 were not acutely toxic to earthworms. Earthworm survival and reproduction were also not adversely affected by chronic exposure to cyflumetofen. Risk was determined based on EECs for the highest use rate scenario of Nealta Miticide (using a soil density of 1.5 g/cm^3 and a 15-cm soil incorporation of the end-use product). The LOC was not exceeded for earthworms (Appendix I, Table19).

Bees (Pollinators): During spray application of the proposed foliar end-use product (Nealta Miticide) adult forager bees may be exposed to spray droplets during flight. Acute contact exposure to cyflumetofen and its end-use product did not result in significant mortality or sublethal effects in honey bees. Based on an exposure estimate of 0.48 µg a.i./bee and a laboratory endpoint of >100 µg a.i./bee for cyflumetofen (for both TGAI and end-use product), the RQ does not exceed the LOC (RQ value of <0.005; Appendix I, Table 19.

Cyflumetofen may be found on pollen and nectar as spray droplets deposited onto open flowers during application of Nealta Miticide insecticide. Acute oral exposure to Nealta Miticide did not result in significant mortality or sublethal effects in honey bees. Based on an exposure estimate of 5.8 µg a.i./bee and a laboratory endpoint of >116 µg a.i./bee for Nealta Miticide, the RQ does not exceed the LOC for adults (RQ value of <0.05; Appendix I, Table 19). No larvae/brood or field studies were submitted on pollinators. Based on the mode of action of cyflumetofen, whereby the action site activity differs between different organisms (allowing for a range of selectivity depending on the organism) cyflumetofen shows a high specificity to the targeted mites (predominantly the Tetranychidae family of mites). Effects on bees, either adults or larvae, are therefore not expected. This is supported by the lack of adverse effects observed with the two beneficial arthropod indicative species, notably one of which is a species of mite. Therefore, no toxicity to bee brood is expected, and no further data are required.

Beneficial arthropods: Exposure of predators and parasites to Nealta Miticide could result from contact with treated plant material or ingestion of a contaminated food source. As the ecotoxicity studies are based on contact exposure, the determination of risk was based on the short-term contact pathway only. It was determined that the LOC (= 2) was not exceeded for the parasitic wasp (*Aphidius rhopalosiphi*) and predaceous mite (*Typhlodromus pyri*) for in-field scenario, and using the maximum seasonal rate of 275.8 g a.i./ha on plants (Appendix I, Table 19). Thus, Nealta Miticide is not expected to pose a risk to beneficial arthropods at the use rate.

Non-target plants: When Nealta Miticide was applied to test plants (monocots and dicots) at an application rate of up to 280-306 g a.i./ha, there were no effects on vegetative vigour. The EC_{25} was greater than the highest test concentrations for all monocot and dicot species tested (ranging 280-306 g a.i./ha). Using the $EEC\_{}_{\text{in-field}}$ of 275.8 g a.i./ha, RQ values were all less than 1.0. Thus, the LOC was not exceeded for plant vegetative vigour (Appendix I, Table 19).

In the seedling emergence study, for the four monocot species that were tested, only oat showed significant adverse effects (reductions in shoot dry weight and length) but no dose-response pattern was observed. For the six dicots that were tested, tomato was the most sensitive species and a dose-response pattern was observed with a 21-day EC_{25} value of 44.0 g a.i./ha (shoot dry weight). Thus, the LOC was exceeded for dicots with a risk quotient of 5.09 (Appendix I, Table 19).

The exceedence of the LOC for dicots triggered the need for a refined assessment to determine risk resulting from off-field exposure of cyflumetofen by spray drift. The application rate was determined by taking into account the amount of spray drift deposition (as a percentage of the application rate) that will result 1 metre downwind from the site of application. Refined risk quotients were recalculated using EECs corrected for the estimated maximum deposition with a fine spray droplet size based on the American Society of Agricultural Engineers (ASAE) classification and based on the application use pattern (6% for ground field sprayer application, 74% drift for early season airblast and 59% drift for late season airblast).

For the field sprayer refined exposure scenario, the LOC based on seedling emergence of non-target terrestrial plants was not exceeded. The LOC was, however, exceeded for the early and late season airblast applications (Appendix I, Table 21). It was determined that buffer zones of 1 metre and 5 metres in size were required for the protection of sensitive terrestrial habitats from spray drift due to application by field sprayer and airblast, respectively. Due to the uncertainty regarding possible adverse effects to monocot species (based on data provided for oat), more information is required. As confirmatory data, the Applicant is requested to submit a new seedling emergence study with oat.

Birds and Mammals: All screening level RQ values for acute and short-term exposures were less than the LOC, while for the reproduction of small birds (increased number of cracked eggs per pen), the risk quotient (RQ) was 1.02 for on-field maximum residues (Appendix I, Table 20). Under field conditions, birds and mammals will be exposed to a vast range of residue concentrations on contaminated food items, and not always the maximum level, as used in the screening assessment. Considering that the birds are going to be exposed to a range of residue concentrations for a prolonged period of time (before and during mating) which will be less than the assumed maximum residue concentration, the likelihood of these effects occurring is small. Therefore, using mean residue concentrations in food items would further reduce the risk quotient for reproduction in small birds to below the LOC ($RQ\_{}_{\text{mean residues}}$ is 0.57). The use of Nealta Miticide is not expected to pose a risk to birds and mammals.

4.2.2 Risks to Aquatic Organisms

Although the use pattern of Nealta Miticide does not include direct application to water, the possibility that aquatic systems will be exposed to cyflumetofen, directly or indirectly, cannot be ruled out. Cyflumetofen may enter the aquatic environment through spray drift and/or runoff.

A screening level risk assessment of cyflumetofen, a formulated product containing this TGAI (Cyflumetofen 20% SC), and the major transformation products A-2, B-1, B-2, AB-1, AB-1 dimer, and AB-11 was undertaken for freshwater and marine aquatic organisms. Screening level EEC values were calculated based on a direct application of the end-use product to water bodies of either 15 cm (seasonal) or 80 cm (permanent). Summaries of aquatic toxicity values and the risk assessment are presented in Appendix I, Tables 22 and 23. A refined risk assessment was conducted to further characterize the risk.

The screening level risk quotients for cyflumetofen were based on the seasonal maximum application rate of Nealta Miticide (two applications of 200 g a.i./ha, at a 14-day interval), and a water DT_{50} value of 18.2 days (which is the 80th percentile of six half-life values [without temperature adjustment], obtained in the aerobic aquatic biotransformation studies). The EECs for cyflumetofen in 15 cm and 80 cm deep water bodies were 212 and 39.7 µg a.i./L, respectively. For the transformation products, the EECs were calculated based on molecular weight ratios with the parent compound.

4.2.2.1 Freshwater Organisms

Invertebrates, Fish, Algae, and Vascular Plants

Cyflumetofen has low solubility in water (28.1µg/L) which limited the range of test concentrations that could be used in the aquatic toxicity studies. With the exception of one study, no effects were observed in any of the test solutions and toxicity values were, therefore, reported as greater than the highest concentration in the test. Consequently, RQs for these studies are reported as being less than a calculated value, and concentrations of cyflumetofen (and RQ values) where a toxic response is actually elicited are unknown. The following test results were, however, used to further characterize the risk. A 28-day toxicity study with juvenile carp and the TGAI produced a result based on observed effects (NOEC = 72 µg a.i./L, reduced growth rate). The RQ was below the LOC for a chronic exposure in 80 cm of water. Furthermore, three acute toxicity studies with a formulated product (Cyflumetofen 20% SC, equivalent to Nealta Miticide), which enhanced the solubility of the TGAI, demonstrated that there were no observed effects at higher concentrations of cyflumetofen, and RQs using these toxicity values were all below the LOC for 80 cm of water.

A refined risk assessment was conducted to further delineate the potential for risk to aquatic systems. The exposure routes of runoff and spray drift were investigated separately. For runoff, a standard aquatic ecoscenario was modelled (Appendix I, Table 25) and LOCs were not exceeded, indicating that freshwater aquatic organisms are not expected to be at risk from cyflumetofen via this route of exposure. Risk quotients still exceeded the LOC for spray drift but, based on the discussion above, they were not calculated with definitive toxicity values (Appendix I, Table 24). Therefore, based on the assessment with the end-use product (LOC values not exceeded), and information that runoff should not pose a risk, cyflumetofen is unlikely to pose a risk to non-target organisms (other than amphibians).

Amphibians

No studies were submitted to assess the acute or chronic toxicity of Nealta Miticide to amphibians. Thus, the risk assessment for amphibians uses surrogate data with fish and an EEC in 15 cm of water, representing a shallow, seasonal water body. The most sensitive toxicity endpoint values from fish toxicity studies (acute study on cold water fish, and 28-day chronic study on juvenile life stage for the common carp) were used as surrogate data for the in-water life-stages of amphibians. The LOC for amphibians is exceeded on a chronic basis. Based on data with the formulated product (Cyflumetofen 20% SC), however, acute risks to amphibians is unlikely (see discussion above) to occur.

In a refined risk assessment, exposure to amphibians via spray drift of cyflumetofen may pose a chronic risk to amphibians (Appendix I, Table 24), while runoff events are not expected to be of concern (Appendix I, Table 25). Overall, there is a need for precautionary label statements, including the requirement of spray buffer zones to protect amphibians. It was determined that spray buffer zones up to 3 meters in size were an adequate mitigative measure.

4.2.2.2 Estuarine and Marine Organisms

Invertebrates, Fish and Algae

Cyflumetofen was not acutely toxic to sheepshead minnow, mysid shrimp, eastern oyster or marine algae (diatom, *Skeletonema costatum*). However, risk RQs calculated at the screening level possibly exceeded the LOC for these non-target freshwater organisms, but were not based on definitive toxicity values (Appendix I, Table 23).

Results from acute freshwater toxicity studies, where a formulated product (Cyflumetofen 20% SC) did not exceed the LOC, were extrapolated to marine and estuarine organisms. Considering this, and that no adverse effects were observed at the tested concentrations in marine studies, the use of Nealta Miticide is unlikely to pose a risk to freshwater organisms at these levels.

A refined assessment further indicated that marine and estuarine organisms are not expected to be at risk from runoff (Appendix I, Table 25). The RQs still exceeded the LOC for spray drift but, based on the discussion above, they were not calculated with definitive toxicity values (Appendix I, Table 24). To conclude, cyflumetofen is unlikely to pose a risk to non-target marine and estuarine organisms.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Formulation Bridging Trials

Efficacy trials were conducted with two different formulations, and most of the trials were not conducted with the formulation proposed for registration; therefore, efficacy data from a total of five field trials were provided to demonstrate equivalent efficacy of the two formulations. Of the five bridging trials, three were conducted against Pacific spider mite (*Tetranychus pacificus*) on grapes in California, one was conducted against twospotted spider mite (*T. urticae*) on pear in Oregon and one was conducted against European red mite (*Panonychus ulmi*) on apple in Michigan. The differences between the two formulations was not expected to affect efficacy and the results of the bridging trials confirmed that efficacy of the two formulations is very similar.

5.1.2 Control of European Red Mite on Pome Fruits

Efficacy data from a total of five field trials were provided to demonstrate control of European red mite on pome fruits (in addition to the formulation bridging trial), all of which were conducted on apple, two in Ontario, two in Washington and one in Pennsylvania. The results of these trials collectively demonstrated control of European red mite on apple trees and provided support for the application rate of 200 g a.i./ha, with evidence of inferior efficacy at lower application rates and no significant improvement in efficacy at double the supported rate.

5.1.3 Control of Twospotted Spider Mite on Pome Fruits

Efficacy data from a total of two field trials were provided to demonstrate control of twospotted spider mite on pome fruits (in addition to the formulation bridging trial), one conducted on apple in North Carolina and the other on pear in California. The results of these trials demonstrated control of twospotted spider mite on apple and pear trees and provided support for the application rate of 200 g a.i./ha, with evidence of inferior efficacy at lower application rates.

5.1.4 Control of McDaniel Spider Mite on Pome Fruits

No efficacy data were submitted for McDaniel spider mite (*tetranychuns mcdanieli*), although this species can be a significant pest of fruit crops in Canada and thus represents a valuable addition to the label claims. Submitted efficacy data for Pacific spider mite, twospotted spider mite and European red mite (as well as citrus red mite [*panonychus citri*], not reviewed here) indicate sufficiently broad efficacy of cyflumetofen against different spider mite species to support a reasonable expectation of similar efficacy against McDaniel spider mite.

5.1.5 Control of Spider Mites on Grape

Efficacy data from a total of three field trials were provided to demonstrate control of spider mites on grape (in addition to the formulation bridging trials), all of which were conducted against Pacific spider mite on grape in California. The results of these trials combined with the bridging trials demonstrated control of Pacific spider mite on grape. Although Pacific spider mite is not a pest in Canada, the demonstrated efficacy of cyflumetofen to control that species on grape as well as the related twospotted spider mite and the European red mite on pome fruits, provides support for the label claims for European red mite, twospotted spider mite, and McDaniel spider mite on grape.

5.1.6 Control of Spider Mites on Strawberry

Efficacy data from a total of four field trials were provided to demonstrate control of spider mites on strawberry, three trials conducted against Pacific spider mite on strawberry in California and one trial conducted against twospotted spider mite on strawberry in Florida. The results of these trials show significant and substantial reductions in numbers of spider mites with treatment at application rates of cyflumetofen at or near 200 g a.i./ha and evidence of inferior efficacy at lower application rates. Two of the four trials, one against Pacific spider mite and one against twospotted spider mite, showed consistently acceptable levels of control. The inferior results of the other two trials extended to the positive control treatments in most assessments, suggesting that the results may reflect factors other than product efficacy. Although Pacific spider mite is not a pest in Canada, the demonstrated efficacy of cyflumetofen to control that species as well as the related twospotted spider mite on strawberry provides support for the label claims for twospotted spider mite and McDaniel spider mite on strawberry.

5.1.7 Control of Twospotted Spider Mite on Tomato

Efficacy data from a single field trial conducted in Mexico were provided demonstrating control of twospotted spider mite on tomato. Although evidence of reduced efficacy at application rates lower than 200 g a.i./ha was very limited, this may be attributed to reapplication at an interval only half as long as the recommended reapplication interval.

5.1.8 Acceptable Efficacy Claims

Sufficient efficacy data were submitted to support use of Nealta Miticide for control of European red mite on pome fruits and grape, control of twospotted spider mite on pome fruits, grape, strawberry and tomato and control of McDaniel spider mite on pome fruits, grape and strawberry. The available efficacy data justify the application rate of 200 g a.i./ha for all uses.

5.2 Phytotoxicity to Host Plants

No evidence of phytotoxicity was reported from any of the efficacy trials, including trials in which the supported application rate was doubled and trials in which various adjuvants were added to the treatments.

5.3 Additional Value Considerations

The active ingredient cyflumetofen is not yet included in the Canadian Grower Priority Database; however, European red mite on grape has been identified as a high priority and twospotted spider mite on strawberry has been identified as an intermediate priority for registration of additional alternative pest control products in Canada.

5.4 Sustainability

5.4.1 Survey of Alternatives

Several alternative active ingredients with different modes of action are registered for proposed uses of Nealta Miticide (Appendix I, Table 26). Most of the alternative active ingredients are registered for use on apple and pear, but only one is registered for use on other pome fruits. Four alternative active ingredients are registered for use one grape and three are registered for use on strawberry, but there are none registered for use on field tomato.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Cyflumetofen is compatible with current management practices and is particularly well suited to integrated pest management because it is specifically active against spider mites and has minimal effects on predatory terrestrial arthropods that are beneficial to pest management. In particular, mites in the family Phytoseiidae are key predators of spider mites and several species of phytoseiid mites have been shown to sustain very low mortality when treated directly with cyflumetofen at the application rate proposed for registration.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Numerous instances of resistance of spider mites to pesticides have been reported, twospotted spider mite and European red mite being the two species in which resistance has been reported most frequently. Spider mites in general may be inherently prone to the development of resistance due to their short life cycles that allow them to undergo several generations within a single growing season. Twospotted spider mite is the most ubiquitous and economically important spider mite species, followed by European red mite, and therefore has had the greatest opportunity to develop resistance due to the extent of pesticide use.

Cyflumetofen is classified by the Insecticide Resistance Action Committee (IRAC) as a member of mode-of-action Group 25. Only one other compound (cyenopyrafen) is included in Group 25 and that active ingredient is not registered in Canada. Bifenazate was once placed in Group 25 but is currently classified as being of uncertain mode of action (IRAC 2013). Thus, cyflumetofen provides a new mode of action that will aid resistance management through rotation with the other modes of action currently available. The use of Nealta Miticide is proposed to be limited to two applications per growing season and additional resistance-management recommendations have been included on the proposed product label.

5.4.4 Contribution to Risk Reduction and Sustainability

The specificity of the activity of cyflumetofen against spider mites reduces risk to non-target organisms, including phytoseiid mites and other beneficial arthropods that contribute to integrated pest management. Cyflumetofen also provides a new mode of action for rotation with currently registered active ingredients to help minimize the potential for development of resistance.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, cyflumetofen and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Cyflumetofen does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 27 for comparison with Track 1 criteria.
- Cyflumetofen does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the "List of Pest control Product Formulants and Contaminants of Health or Environmental Concern" maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: "List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern" and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. "Part 1 Formulants of Health or Environmental Concern," "Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions" and "Part 3 Contaminants of Health or Environmental Concern."

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

- Technical grade cyflumetofen does not contain any formulants or contaminants of environmental concern identified in the *Canada Gazette*.
- The end-use product Nealta Miticide has, as a component, the preservative 1,2-benzisothiazoline-3-one, which may contain low levels of polychlorinated dibenzodioxins and furans (TSMP Track 1). As the levels are low, the use of this preservative was recently re-evaluated and found to be acceptable, and because the input of dioxins into the environment from pesticides is being managed as outlined in the PMRA Regulatory Directive DIR99-03 for the implementation of TSMP, no further action is required.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for cyflumetofen is adequate to define the majority of toxic effects that may result from exposure. There was no evidence of genotoxicity. Increased incidences of testicular Leydig cell tumours and thyroid c-cell tumours were observed in male rats after longer-term oral dosing in the confirmatory carcinogenicity study; however, there was no evidence of carcinogenicity in mice or female rats. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies, although a serious endpoint (malformations) was noted in rabbit fetuses at a maternally toxic dose. There was no effect on reproductive performance or outcome. Cyflumetofen is not neurotoxic or immunotoxic. In short-term and chronic studies on laboratory animals, the primary effects in all species following all durations of dosing were changes to the adrenal glands. Changes to the liver, kidney, ovaries, and testes were observed to a lesser extent in the overall database. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

The nature of the residue in plants and animals (ruminants only) is adequately understood. The residue definition for risk assessment and enforcement are cyflumetofen in plants and cyflumetofen and the B-1 metabolite for ruminants. The proposed use of cyflumetofen on pome fruits (CG 11-09), grapes, strawberries, and tomatoes and the importation of treated citrus fruits (CG 10-revised) and tree nuts (CG 14-11) into Canada does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs.

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[8] DIR2006-02, PMRA *Formulants Policy and Implementation Guidance Document*.

Mixers, loaders, applicators and workers entering treated areas are not expected to be exposed to levels of Nealta Miticide that may result in unacceptable risk when Nealta Miticide is used according to label directions. The personal protective equipment and exposure mitigative statements on the product label are adequate to protect workers.

PYO acute residential exposure to general public is not expected to result in unacceptable risk when Nealta Miticide is used according to label directions.

Residential exposure to individuals contacting treated trees is not expected to result in unacceptable risk if Nealta Miticide is applied to residential fruit trees.

7.2 Environmental Risk

Cyflumetofen is non-persistent in soil and aquatic systems, is not mobile in the environment and is not expected to volatilize to the atmosphere. Cyflumetofen exposure may present a risk to non-target terrestrial plants and freshwater amphibians from the use of Nealta Miticide. To minimize the potential for spray drift exposure, spray buffer zones between the treated area and downwind terrestrial or aquatic areas will be required. The width of these spray buffer zones will be specified on the product label. Cyflumetofen presents a negligible risk to other non-target terrestrial and aquatic organisms at the proposed use rates. No environmental risk was identified from exposure to cyflumetofen's major transformation products.

7.3 Value

Nealta Miticide has value for control of European red mite, twospotted spider mite and McDaniel spider mite on pome fruits, grapes, strawberries and tomatoes. Control of European red mite on grape and twospotted spider mite on strawberry have been identified as priorities for Canadian growers. The active ingredient cyflumetofen provides a new mode of action with particular value for resistance management.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Cyflumetofen Technical and Nealta Miticide, containing the technical grade active ingredient cyflumetofen, to control European red mite, twospotted spider mite and McDaniel spider mite on pome fruits, grape, strawberry, and tomato.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

♂	male
♀	female
µg	micrograms
µM	micromolar
^{14}C	radioactive carbon
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
APTT	activated partial thromboplastin time
AR	applied radioactivity
ARfD	acute reference dose
ASAE	American Society of Agricultural Engineers
atm	atmosphere
ATPD	area-treated-per-day
AUC	Area Under the Concentration Curve
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CG	Crop group
cm	centimetre(s)
cm^2	square centimetres
cm^3	cubic centimetres
CDN	Canadian
CO_2	carbon dioxide
CSG	Crop Sub-group
d	day(s)
DAT	days after treatment
DEEM	Dietary Exposure Evaluation Model
DEREK	Deductive Estimation of Risk of Existing Knowledge
DFR	dislodgeable foliar residue
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population

EC_{50}	effective concentration on 50% of the population
EDE	estimated dietary exposure
EEC	estimated environmental concentration
ELISA	enzyme-linked immunosorbent assay
F_1	first generation
F_2	second generation
fc	food consumption
FDA	*Food and Drugs Act*
FIR	food ingestion rate
FOB	functional observation battery
FSH	follicle stimulating hormone
g	gram(s)
GB	ground boom
GD	gestation day
ha	hectare(s)
HAFT	highest average field trial
HDPE	high-density polyethylene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high-performance liquid chromatography with tandem mass spectrometry
hr(s)	hour(s)
IgM	immunoglobulin M
IORE	Indeterminate Order Rate Equation
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC	liquid chromatography
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LH	luteinising hormone
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate at 50%
m^3	square metres
M^3	cubic metres
M/L/A	mixer, loader, applicator
MAS	maximum average score

Max	maximum
mg	milligram(s)
Min	minimum
MIS	maximum irritation score
mL	millilitre
MOA	mode of action
MOE	margin of exposure
mol	molecule
MRL	maximum residue limit
MS	mass spectrometry
MW	molecular weight
N/A	not applicable
N/R	not required
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
P_0	parental generation
PBI	plant back interval
PHED	Pesticide Handlers Exposure Database
PHI	pre-harvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PYO	pick your own
RAC	raw agricultural commodity
REI	restricted entry interval
rel	relative
RQ	risk quotient
RSD	relative standard deviation
SC	soluble concentrate
SFO	single first-order
SRBC	sheep red blood cells
STMR	supervised trial mean residue
STMdR	supervised trial media residue
SU	suspension
TC	transfer coefficient
TFA	trifluoroacetic acid
TGAI	technical grade active ingredient
TRR	total radioactive residue

TSMP	Toxic Substances Management Policy
U.K.	United Kingdom
U.S.	United States
UDS	unscheduled DNA synthesis
UF	uncertainty factor
UPLC-MS/MS	Ultra-high-performance liquid chromatography with tandem mass spectrometry
UPLC-UV	Ultra-high-performance liquid chromatography with UV detection
UV	ultraviolet
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	D1002	Cyflumetofen	UPLC-MS/MS 448.2 → 173.0	0.01 ppm	2146748, 2146749
		B-1	189.1 → 69.0		
		B-3	190.0 → 130.0		
		A-2	174.1 → 147.1		
		AB-1 dimer	689.4 → 288.2		
Sediment	N/A	AB-1	UPLC-MS/MS 344.2 → 304.0	100 mg/kg	2146760
	The soil methods may also be extended to sediment				
Water	N/A	Cyflumetofen	HPLC-MS/MS 448.3 → 173.1	0.1 µg/L	2146756
		B-1	UPLC-MS/MS 189 → 145		2146754
		B-3	UPLC-MS/MS 190.1 → 130.0		2146755
		AB-1	UPLC-UV 263 nm	0.005 mg/L	2146758
	D1307	AB-1	UPLC-MS/MS 344 → 304	0.05 µg/kg	2355564
		A-2	174 → 147	0.05 µg/kg	
		A-12	179 → 57	0.5 µg/kg	
Plant	D1003	Cyflumetofen, B-1	Enforcement	0.01 ppm each analyte	2146742 2146740
Animal	D1202	Cyflumetofen and B-1	Enforcement	0.01 ppm each analyte in tissue 0.001 ppm each analyte in milk	2241113

Table 2 Toxicity Profile of the End-use Product Containing Cyflumetofen (Nealta Miticide)

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Wistar rats (♀) PMRA #2145864	LD_{50} >2000 mg/kg bw (♀) Low toxicity
Acute dermal toxicity Wistar rats PMRA #2145866	LD_{50} >5000 mg/kg bw Low toxicity

Study Type/Animal/PMRA #	Study Results
Acute inhalation toxicity (nose-only) Wistar rats PMRA #2145868	LC_{50} >5.18 mg/L Low toxicity
Dermal irritation NZW rabbits PMRA #2145870	Very slight erythema and moderate edema were observed at 1 hour. Severity decreased over time and all eyes were normal at 72 hours. MAS = 0.44, MIS = 1.67 (0 and 1 hr) Minimally irritating
Eye irritation NZW rabbits (♀) PMRA #2145871	At 1 hour, slight conjunctival redness was observed. Eyes were normal at 24 hours. MAS = 0, MIS = 2 (1 hr) Non-irritating
Dermal sensitization (LLNA) CBA/CaCrl mice (♀) PMRA #2145876	Non-sensitizer

Table 3 Toxicity Profile of Technical Cyflumetofen

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Radiolabelled cyflumetofen (4-tert-butylphenyl (A-ring) or α, α, α-trifluoro-o-tolyl group (B-ring)) was administered to Fischer rats as a single oral dose at 3 or 250 mg/kg bw or as repeated oral doses at 3 mg/kg bw. In addition, male and female bile-cannulated Fischer rats were administered a single oral dose of radiolabelled cyflumetofen at 3 or 250 mg/kg bw. Excreta, blood and tissues were collected from the treated animals; radioactivity was quantified and metabolites were isolated and identified when possible. Absorption rates for the A-ring group were higher for the low-dose group (68% and 71% in males and females, respectively) than for the high-dose group (46% for both males and females). For the B-ring group, the absorption rate was higher in females (78%) than males (69%) at the low-dose, but higher in males (44%) than females (35%) at the high-dose. In plasma, T_{max} occurred within 1 hour at the low-dose indicating rapid absorption. Absorption was slightly slower at the high-dose, with T_{max} reached at 1-4 hours post-dosing. At the high-dose, females demonstrated higher C_{max} and AUC values than males for both radiolabels. The AUC values at the high-dose were approximately 15-16 and 36-38 times the AUC at the low-dose for males and females, respectively. These values are much lower than the 83-fold difference in dose levels, indicating saturation of absorption following high-dose administration. In addition, a comparison	

Study Type/Animal/PMRA #	Study Results
of the results following single and repeated low-dose administration indicated the potential for saturation of absorption with repeated low-dose administration. At 72 hours post-dosing, the total radioactivity recovered from the tissues and carcass accounted for 0.3-2.5% of the administered dose (AD), with lower levels detected in the high-dose groups than in the low-dose groups. The highest levels of radioactivity were detected in the liver, kidney, GIT and carcass. There were no significant differences between males and females at either dose. Residue levels did not appreciably increase following repeated dosing, indicating little potential for accumulation. For all test groups, the plasma radioactivity levels declined rapidly and followed biphasic first-order kinetics. Elimination half-lives from plasma for the A- and B-ring groups ranged from 12-16 hours in the low-dose groups and from 13-20 hours in the high-dose groups for both sexes, with no consistent patterns in terms of differences related to sex, dose or radiolabel position. For the low-dose groups, biliary, urinary and fecal excretion accounted for approximately 25-37%, 29-51% and 6-17% of the AD, respectively. For the high-dose groups, biliary, urinary and fecal excretion accounted for approximately 18-32%, 11-24% and 34-41% of the AD, respectively. At the low-dose, 90-96% of the radioactivity excreted in urine was eliminated within 24 hours after dosing, whereas excretion was slower at the high-dose (74-88%). At both low- and high-doses, 60-89% of the radioactivity excreted in feces was eliminated within 24 hours of dosing. The parent compound was not identified in urine. In feces, the parent compound was found at low levels (2-4%) in the low-dose groups, but at higher levels (54-66%) in the high-dose groups following administration of both labels. The only metabolite detected in feces was B-1, which was detected at much higher levels in the low-dose groups than in the high-dose groups. There were no appreciable residues measured in expired air. ^{14}C-cyflumetofen was metabolized in the rat primarily by hydrolytic cleavage of the trifluoromethylbenzoyl moiety resulting in metabolite B-1 (trifluoromethylbenzoic acid) and A-18. Another minor pathway included successive hydroxylation of the tert-butyl side chain. Plasma kinetics were also determined following administration of a single oral dose of radiolabelled cyflumetofen (tolyl ring only) to CD1 mice at levels of 50, 250, 500 or 1000 mg/kg bw. In plasma, the first T_{max} was observed at 0.5 to 1 hour post-doing, with females showing a second T_{max} at 2 (250 mg/kg bw) or 8 hours (50, 500, 1000 mg/kw bw) post-dosing. After 0.5 hours in males or 2 or 8 hours in females, radioactivity in plasma rapidly declined. Females exhibited a higher AUC than males (1.4-2.0 times) indicating higher internal doses.	
Acute Oral Toxicity (Fixed Dose Method) Wistar Rat (♀) PMRA# 2146782	No deaths. LD_{50} >2000 mg/kg bw Low toxicity.

Study Type/Animal/PMRA #	Study Results
Acute Dermal Toxicity Wistar Rat PMRA# 2146783	No deaths. LD_{50} >5000 mg/kg bw Low toxicity.
Acute Inhalation (nose-only) Toxicity Wistar Rat PMRA# 2146784 and 2146785	No deaths. LC_{50} >2.65 mg/L Low toxicity.
Eye Irritation New Zealand White Rabbit (♀) PMRA# 2146787	MAS (24, 48 and 72 hrs) = 1.8 MIS (1 hour) = 3.33 Minimally irritating.
Dermal Irritation New Zealand White Rabbit (♂) PMRA# 2146786	MAS (24, 48 and 72 hrs) = 0 MIS (all timepoints) = 0 Non-irritating.
Dermal Sensitization (Maximization Test) Dunkin Hartley Guinea pig (♀) PMRA# 2146788	Positive. Potential dermal sensitizer.
28-day Oral Toxicity (diet) CD-1 mouse PMRA# 2146799	NOAEL = 135/150 mg/kg bw/day (1000 ppm) LOAEL = 663/763 mg/kg bw/day: ↑ adrenal wt, adrenal cortical cell hypertrophy; adrenal cortical cell vacuolation (♀)
90-day Oral Toxicity (diet) CD-1 mouse PMRA# 2146801	NOAEL (♀) = 150 mg/kg bw/day (1000 ppm) NOAEL (♂) = 348 mg/kg bw/day (3000 ppm) LOAEL (♀) = 447 mg/kg bw/day: adrenal cortical cell vacuolation LOAEL (♂) = 1200 mg/kg bw/day: ↑ size of adrenals, ↑ adrenal wt
14-day Oral Toxicity (diet) Fischer rat PMRA# 2146793	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Adverse effects at ≥ 101/105 mg/kg bw/day included: adrenal cortical cell vacuolation; ↓ potassium, ↑ rel liver wt (♂); ↑ adrenal wt, vacuolation of ovarian interstitial cells (♀)

Study Type/Animal/PMRA #	Study Results
28-day Oral Toxicity (diet) Fischer rat PMRA# 2146792	NOAEL = 37.6/40.8 mg/kg bw/day (500 ppm) LOAEL = 75.1/79.8 mg/kg bw/day: vacuolation of adrenal cortical cells; ↓ cholesterol, triglycerides, ↑ liver wt, hepatocyte hypertrophy (♂); ↑ adrenal wt, vacuolation of ovarian interstitial cells, adrenal cortical cell hypertrophy (♀)
90-day Oral Toxicity (diet) Fischer rat PMRA# 2146797	NOAEL = 16.5/19.0 mg/kg bw/day (300 ppm) LOAEL = 54.5/62.8 mg/kg bw/day: adrenal cortical cell vacuolation, ↑ rel liver wt (♂); ↓ globulin (G), ↑ A/G ratio, ↑ adrenal (A) wt, vacuolation of ovarian interstitial cells, adrenal cortical cell hypertrophy (♀) FOB: There were no treatment-related findings.
28-day Oral Toxicity (capsule) Beagle dog PMRA# 2146795	NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day: ↑ adrenal wt, adrenal cortical cell vacuolation
90-day Oral Toxicity (capsule) Beagle dog PMRA# 2146803	NOAEL = 300 mg/kg bw/day LOAEL = 1000 mg/kg bw/day: ↓ bwg, adrenal cortical cell vacuolation; ↑ adrenal wt, ↓ food efficiency (♂); ↓ food consumption (♀)
1-year Oral Toxicity (capsule) Beagle dog PMRA# 2146806	NOAEL = 30 mg/kg bw/day LOAEL = 300 mg/kg bw/day: adrenal cortical cell vacuolation, adrenal cortical cell degeneration, adrenal interstitial cell fibrosis, lymphocyte cell infiltration of adrenals; infiltration of brown pigment-laden macrophages in adrenals (♂); ↑ size of adrenals (♀)
28-day Dermal Toxicity Wistar rat PMRA# 2146807	NOAEL = 1000 mg/kg bw/day LOAEL = 300 mg/kg bw/day: ↑ kidney wt (♂) without histopathological correlate. No treatment related adverse effects (systemic or irritation).
Oncogenicity (diet) CD-1 mouse PMRA# 2146824	NOAEL = 156/144 mg/kg bw/day (1500 ppm) LOAEL = 537/483 mg/kg bw/day: ↑ adrenal cortical cell vacuolation; ↑ adrenal weights (♂) No evidence of carcinogenicity; animals could have tolerated higher dose levels.

Study Type/Animal/PMRA #	Study Results
Oncogenicity (diet) CD-1 mouse PMRA# 2340604	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Adverse effects at 1143/1132 mg/kg bw/day (10,000 ppm) included: adrenal cortical cell vacuolation, deposition of brown pigment in the cortico-medullary junction of the adrenals; ↑ adrenal weight, enlarged spleen, extramedullary hematopoiesis in the spleen (♀) No evidence of carcinogenicity.
1-year Chronic Oral Toxicity (diet) Fischer rat PMRA# 2146817	NOAEL = 18.8/23.3 mg/kg bw/day (500 ppm) LOAEL = 56.8/69.2 mg/kg bw/day (1500 ppm): diffuse vacuolation of adrenal cortical cells, atrophy of seminal vesicles and coagulating gland (♂); ↑adrenal wt, ↑ ovarian wt, hypertrophy of adrenal cortical cells, vacuolation of ovarian interstitial gland cells (♀)
1-year Chronic Oral Toxicity (diet) Fischer rat PMRA# 2266332	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Adverse effects at 250/319 mg/kg bw/day (6000 ppm) included: ↓ bwg, ↓ platelets, fibrinogen, ↑ BUN, ↑ kidney wt, liver wt, adrenal wt; ↑ prothrombin time, APTT, white adrenals, ↑ diffuse adrenal cortical cell vacuolation, ↑ testicular interstitial cell hyperplasia, ↑ pancreatic acinar cell atrophy, ↑ atrophy, softening and spots in the testis (♂); soiled fur in external genital area, ↓ bw, enlarged adrenals, ↑ diffuse adrenal cortical cell hypertrophy, ↑ focal adrenal cortical cell vacuolation, ↑ vacuolation of ovarian interstitial gland cells (♀)
Carcinogenicity (diet) Fischer rat PMRA# 2146822	NOAEL = 16.5/20.3 mg/kg bw/day (500 ppm) LOAEL = 49.5/61.9 mg/kg bw/day: adrenal cortical cell hypertrophy and hyperplasia; luminal dilatation of uterine horn gland (♀) No evidence of carcinogenicity; animals could have tolerated higher dose levels
Carcinogenicity (diet) Fischer rat PMRA# 2351972 PMRA# 2383789	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Adverse effects at 220/287 mg/kg bw/day (6000 ppm) included: ↓ bw, ↑ adrenal wt, diffuse hypertrophy of adrenal cortical cells, focal vacuolation of adrenal cortical cells; ↓ bwg,

Study Type/Animal/PMRA #	Study Results
	↓ differential leukocyte count, ↑ testis wt, liver wt (rel), ↑ focal atrophy of pancreatic acinar cells, ↑ atrophy of epididymides, ↑ masses in testis (♂); tactile hair loss, ↑ ovary wt, liver wt, diffuse vacuolation of the adrenal cortical cells (♀) Neoplastic lesions: ↑ incidence of thyroid c-cell tumours (carcinoma, and adenoma and carcinoma combined) and testicular interstitial cell tumours in males. Incidence of thyroid tumours (n=50): adenoma 11,15; carcinoma 9, 15; combined 19, 28 Incidence of testicular tumours (n=50): 38, 48.
Range-Finding Developmental Toxicity (gavage) Wistar rat PMRA# 2146829	A NOAEL and LOAEL were not established as this study was considered to be supplemental. No treatment-related effects were noted at the high-dose of 1000 mg/kg bw/day.
Developmental Toxicity (gavage) Wistar rat PMRA#2146830	Maternal NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day: ↑ adrenal wt, adrenal cortical cell vacuolation Developmental NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day: ↑ incomplete ossification (sternal centra) No evidence of sensitivity of the young.
Range-Finding Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 2146832	A NOAEL and LOAEL were not established as this study was considered to be supplemental. No treatment-related effects were noted at the high-dose of 1000 mg/kg bw/day.
Developmental Toxicity (gavage) New Zealand White rabbit PMRA# 2146831	Maternal NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day: ↓ bwg (GD 6-29), ↓ abs liver wt Developmental NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day: ↑ # ossified thoracic vertebrae and ribs, ↓ # ossified lumbar vertebrae, ossified xiphoids

Study Type/Animal/PMRA #	Study Results
	At 1000 mg/kg bw/day, malformations (bent paws) were observed in the presence of maternal toxicity (↓ fc (GD 6-29), ↓ abs adrenal wt). No evidence of sensitivity of the young.
Range-Finding Reproductive Toxicity (diet) Wistar rat PMRA# 2146826	A NOAEL and LOAEL were not established as this study was considered to be supplemental. Parental Toxicity Adverse effects at 57.1/107.8 mg/kg bw/day included: adrenal cortical cell vacuolation (♂); adrenal cortical cell hypertrophy (♀) Offspring Toxicity Adverse effects at 57.1/107.8 mg/kg bw/day included: adrenal cortical cell hypertrophy Reproductive Toxicity No treatment-related effects at the high dose of 107.8 mg/kg bw/day.
Reproductive Toxicity (diet) Wistar rat PMRA# 2146828	Parental Toxicity NOAEL = 9.21/13.8 mg/kg bw/day (150 ppm) LOAEL = 30.6/46.6 mg/kg bw/day: ↑ adrenal wt, adrenal cortical cell hypertrophy (♀) Offspring Toxicity NOAEL = 9.21/13.8 mg/kg bw/day (150 ppm) LOAEL =30.6/46.6 mg/kg bw/day: ↑ adrenal wt (F1, F2), adrenal cortical cell hypertrophy (F1); adrenal cortical cell hypertrophy (F2 ♂); marginal delays in sexual maturation (F1 ♀; 29.5 days vs. 30.7 days at the mid-dose, 29.5 days vs. 31.0 days at the high-dose) Reproductive Toxicity NOAEL (♂) ≥ 89.4 mg/kg bw/day (1500 ppm) NOAEL (♀) = 46.6 mg/kg bw/day (500 ppm) LOAEL (♀) = 141.1 mg/kg bw/day: ↓ estradiol, FSH, progesterone (F1 ♀), slight ↑ in estrous cycle length (F1 ♀; 4.0 days vs. 4.2 days), ↑ ovary wt (P ♀), vacuolation of ovarian interstitial cell (F1 ♀) No effect on reproductive performance. No evidence of sensitivity of the young.

Study Type/Animal/PMRA #	Study Results
Bacterial Reverse Mutation Assay *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP_2uvrA PMRA# 2146809	Negative
In vitro Mammalian Gene Mutation Assay L5178Y Mouse Lymphoma cells PMRA# 2146813	Positive at cytotoxic and precipitating concentrations only (90 µg/mL -S9 and 140 µg/mL +S9) Negative
In vitro Chromosome Aberration Assay Chinese hamster V79 cells PMRA# 2146811	Negative
In vitro Mammalian Chromosome Aberration Assay Chinese hamster CHL cells PMRA# 2146812	Negative
Mouse Micronucleus Test CD-1 mouse PMRA# 2146814	Negative
In vivo UDS Test Wistar rat hepatocytes PMRA# 2146815	Negative
Acute Oral Neurotoxicity (gavage) Wistar rat PMRA# 2146835	NOAEL ≥ 2000 mg/kg bw 2000 mg/kg bw: No treatment-related effects. No evidence of neurotoxicity.

Study Type/Animal/PMRA #	Study Results
90-day Oral Neurotoxicity (diet) Wistar rat PMRA# 2146836	NOAEL = 30/41 mg/kg bw/day (500 ppm) LOAEL = 89/99 mg/kg bw/day: adrenal cortical cell vacuolation; ↑ adrenal wt (♀) No evidence of neurotoxicity.
Immunotoxicity (diet) (28-days) Wistar Rat PMRA# 2146780	NOAEL = 33 mg/kg bw/day LOAEL =107 mg/kg bw/day: ↑ adrenal wt, adrenal cortical cell vacuolation No signs of immunotoxicity observed (ELISA – serum IgM response to SRBC)
In vitro Aromatase (Human Recombinant) PMRA# 2199468	Negative for inhibition of CYP19 aromatase activity.
In vitro Estrogen Receptor Transcriptional Activation (HeLa-9903) PMRA# 2199467	Negative for estrogen transcriptional activation.
In vitro Steroidogenesis Assay (H295R Cells) PMRA# 2199466	Increased estradiol concentration at ≥ 5 μM (tests 1-3). Decreased testosterone concentration at ≥ 1 μM (tests 1 and 2), and at ≥ 5 μM (test 3).
In vitro Estrogen Receptor Binding Assay (rat uterine cytosol) PMRA# 2199465	Non-interactive with the estrogen receptor.
In vitro Androgen Receptor Binding Assay (rat prostate cytosol) PMRA# 2199464	Non-binder with the androgen receptor.

Table 4 Toxicity Profile of Metabolites B-1 and B-3 and Impurity AB-13

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
DEREK Toxicity Prediction Assessment of B-1 (metabolite) PMRA# 2146837	No structural alerts found for any of the endpoints covered by DEREK.

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity with B-1 (metabolite) (Acute Toxic Class) Wistar Rat PMRA# 2146848	No deaths. LD_{50} >2000 mg/kg bw Low toxicity.
Bacterial Reverse Mutation Assay with B-1 (metabolite) *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP_2uvrA PMRA# 2146844	Negative.
In vitro Chromosome Aberration Assay with B-1 (metabolite) Human peripheral lymphocytes PMRA# 2146847	Negative.
In vivo UDS Test with B-1 (metabolite) Wistar rat hepatocytes PMRA# 2146839	Negative.
In vitro Mammalian Gene Mutation Assay with B-1 (metabolite) L5178Y Mouse Lymphoma cells PMRA# 2146846	Positive (- S9 mix only) following 24 hour treatment only.
DEREK Toxicity Prediction Assessment of B-3 (metabolite) PMRA# 2146838	No structural alerts found for any of the endpoints covered by DEREK.

Study Type/Animal/PMRA #	Study Results
Bacterial Reverse Mutation Assay with B-3 (metabolite) *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP_2uvrA PMRA# 2146840	Positive (- S9 mix) in S. typhimurium strain TA100 only.
In vitro Chromosome Aberration Assay with B-3 (metabolite) Human peripheral lymphocytes PMRA# 2146841	Negative.
In vitro Mammalian Gene Mutation Assay with B-3 (metabolite) L5178Y Mouse Lymphoma cells PMRA# 2146842	Positive (- S9 mix) following 24 hr treatment only.
In vivo UDS Test with B-3 (metabolite) Wistar rat hepatocytes PMRA# 2146843	Negative. Preliminary test: 1 male was dosed at each of the following levels: 100, 250, 500, 1000 or 2000 mg/kg bw. Two males were dosed at 350 mg/kg bw. Results: The animal dosed at 2000 mg/kg bw died within 3.5 hours of dosing. The animals at 500 at 1000 mg/kg bw were sacrificed for humane reasons at 4 hours post-dosing. The two animals at 350 mg/kg bw were lethargic and ataxic one hour following dosing, with ventral recumbency in one animal at 3 hours post-dosing. These signs lasted until termination at 24 hours. At 250 mg/kg bw, lethargy and ataxia was observed at 1 hour post-dosing, with full recovery by 20 hours. There were no treatment-related clinical signs observed at 100 mg/kg bw.

Study Type/Animal/PMRA #	Study Results
DEREK Toxicity Prediction Assessment of AB-13 (impurity) PMRA# 2146662	The DEREK analysis predicted that AB-13 might cause α-2-μ-globulin nephropathy in rats. Kidney effects (α-2-μ-globulin nephropathy) are known to be sex- and species-specific and are not considered to be a hazard to human health Developmental and testicular toxicity is predicted to be plausible due to the presence of the monomethyl glycol ether moiety which can be released from the ester function. As this moiety is also present in the chemical structure of the parent compound cyflumetofen, the effect of this moiety has been tested in the toxicity testing performed with cyflumetofen.
Acute Oral Toxicity with AB-13 (impurity) (Acute Toxic Class) Wistar Rat PMRA# 2146665	No deaths. LD_{50} >2000 mg/kg bw Low toxicity.
Bacterial Reverse Mutation Assay with AB-13 (impurity) *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2uvrA PMRA# 2146661	Negative.
In vitro Mammalian Gene Mutation Assay with AB-13 (impurity) L5178Y Mouse Lymphoma cells PMRA# 2199463	Negative.
In vitro Chromosome Aberration Assay with AB-13 (impurity) Human peripheral lymphocytes PMRA# 2146664	Negative.

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Cyflumetofen

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Not required. A relevant endpoint of concern was not identified in the database.		
Acute dietary females ages 13-49	Rabbit developmental toxicity study	250 mg/kg bw/day: malformations (paws bent downward) at 1000 mg/kg bw/day	300
	ARfD = 0.8 mg/kg bw		
Repeated dietary	2-year rat oncogenicity and 90-day oral rat studies	16.5 mg/kg bw/day: adrenal toxicity	100
	ADI = 0.2 mg/kg bw/day		
Short-term dermal[2]	Rabbit developmental toxicity study	250 mg/kg bw/day: malformations (paws bent downward) at 1000 mg/kg bw/day	300
Intermediate and long-term dermal[2]	2-year rat oncogenicity and 90-day oral rat studies	16.5 mg/kg bw/day: adrenal toxicity	100
Inhalation – all durations[3]	2-year rat oncogenicity and 90-day oral rat studies	16.5 mg/kg bw/day: adrenal toxicity	100
Aggregate (pick your own) – general population	Not required. A relevant endpoint of concern was not identified in the database.		
Aggregate (pick your own) – females ages 13-49	Rabbit developmental toxicity study	250 mg/kg bw/day: malformations (paws bent downward) at 1000 mg/kg bw/day	300
Cancer	Testicular interstitial cell tumours and thyroid c-cell tumours observed in male rats; a threshold approach to cancer risk assessment was necessary due to limitations in the available data		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 11% was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Mixer, Loader and Applicator Exposure and Risk

Crop	M/L/A scenario	Application rate (kg a.i./ha)	Area treated per day (ha)[1]	Dermal M/L PHED exposure (µg/kg a.i.)[2]	Dermal applicator PHED exposure (µg/kg a.i.)[2]	Dermal exposure (mg/kg bw/day)[3]	Dermal MOE[5] target MOE (100)	Inhalation M/L PHED exposure (µg/kg a.i.)[2]	Inhalation applicator PHED exposure (µg/kg a.i.)[2]	Inhalation exposure (mg/kg bw/day)[4]	Inhalation MOE[5] Target MOE (100)	Combined MOE[6](dermal + inhalation) Target (100)
Grape Pome fruit (apple, pear)	Air blast (farmer short-term)	0.2	20	51.14	828.22	0.0048	51,690	1.6	5.8	0.00037	44,595	N/A
Grape Pome fruit	Air blast (custom intermediate-term)	0.2	20	51.14	828.22	0.0048	3,412	1.6	5.8	0.00037	44,595	3,169
Strawberry Tomato	Farmer GB*, open-cab	0.2	26	51.14	32.98	0.00060	4,15,657	1.6	0.96	0.000166	99,159	N/A
Strawberry Tomato	Custom GB* open cab	0.2	26	51.14	32.98	0.00060	27,433	1.6	0.96	0.000166	99,159	21,488

* GB = ground boom

[1] Area treated per day defaults (PMRA ATPD SOP, revised, July 2010).

[2] Dermal/Inhalation Unit Exposures from PHED: (1) mixer/loader, wearing a long sleeved shirt, long pants and chemical resistant gloves, Scenario 3a: liquid; open pour mix/load; (2) Applicator, wearing a long sleeved shirt and long pants and no gloves, Scenario 11, Ground boom open cab application, or Scenario 9, Air blast application, open cab.

[3] Daily Dermal exposure (mg/kg bw/day) = (area treated per day × application rate) × PHED dermal unit exposure (Mixer/Loader + Applicator) × 11% dermal absorption × 0.001 mg/µg/80 kg bw

[4] Daily Inhalation exposure (mg/kg bw/day) = (area treated per day × application rate) × PHED inhalation unit exposure (Mixer/Loader + Applicator) × 100% inhalation exposure × 0.001mg/µg/80kg bw

[5] Dermal MOE for farmers (Short-term dermal exposure) = NOAEL of 250 mg/kg/day from rabbit developmental study /Dermal Exposure (mg/kg bw/day); target MOE 300; Or Dermal MOE for custom applicators (intermediate-term dermal exposure) = NOAEL of 16.5 mg/kg/day from 90 days oral study/Dermal Exposure (mg/kg bw/day); target MOE 100; Or Inhalation MOE for farmers (short - term)/custom applicators (intermediate-term): NOAEL of 16.5 mg/kg/day from 90 days oral study/Inhalation Exposure (mg/kg bw/day); Target MOE 100

[6] Combined (dermal + inhalation) MOEs for intermediate-term exposures only = 1 / [(1/MOE dermal) + (1/MOE inhalation)]. Target MOE is 100

Table 7 Postapplication Exposure and Risk

Crop	Re-entry activity	TC[1] (cm^2/hr)	DFR[2] ($\mu g/cm^2$)	Dermal Exposure[3] (mg/kg bw/day)	Short-term Dermal MOE[4] Target 300	Intermediate-term Dermal MOE[4] Target 100
Grape (table, raisin)	Cane turning and girdling	19300	0.268	0.0569	4,394	290
Grape (wine, juice)	Hand harvesting	8500	0.268	0.0251	9,977	658
Pome fruit	Thinning	3000	0.6144	0.0203	12,330	814
Strawberry	Hand harvesting	1100	0.6144	0.0074	33,628	2,219
Tomato	Handset irrigation	1750	0.6144	0.0118	21,138	1,395

[1] TC= Transfer coefficients from PMRA Agriculture TC Table

[2] DFR = for grapes: average peak residue of 0.268 $\mu g/cm^2$ detected at the Pennsylvania site from the submitted DFR study. For all other crops: PMRA default DFR after two applications at the interval of 14 days, as 25% of the maximum application rate (200 g a.i./ha or 2 $\mu g/cm^2$) retained on foliage for dislodging on the day of application and 10% dissipation/degradation loss per day after each application.

[3] Dermal Exposure (mg/kg bw/day) = (DFR × TC × 8 hours/day × 11% dermal absorption/80 kg bw × 1000 (µg/mg).

[4] MOE = LOAEL of 250 mg/kg bw/day from rabbit developmental study/Short-term Dermal Exposure, Target MOE = 300; or, Intermediate- to Long-term Dermal Exposure: NOAEL of 16.5 mg/kg bw/day from 90 days oral study (adrenal glands effects), Target MOE = 100

Table 8 PYO Aggregated Acute Exposure and Risk

Crop	Subpopulation	Acute dermal exposure[1] (mg/kg bw/day)	Acute dermal MOE[3]	Acute dietary exposure[2] (mg/kg bw/day)	Acute dietary MOE[3]	Total aggregate MOE[4] Target MOE 300
Apples	Females of 13-49 years of age	0.0027	91,156	0.00099	253,855	67072
Pears		0.0027	91,156	0.000803	311,456	70,517
Strawberries		0.0022	1,16,017	0.001362	1,83,598	71,093

[1] Acute Dermal Exposure (mg/kg bw/day)= default DFR of 0.6144 $\mu g/cm^2$ × TC of 1400 (apple/pear) or 1100 (strawberry in) cm^2/hour for hand harvesting fruit × 2 hours./day PYO exposure ×11% dermal absorption × 0.001 mg/µg)/bw of 69 kg (females 13-49)

[2] Acute dietary (commodity-specific) exposure = from the Dietary Exposure Assessment, 95th percentile user-only, maximum residue value, fresh commodity-only, commodity-specific values presented as one-day exposure (mg/kg bw/day); females 13-49, body weight 69 kg

[3] Acute dermal MOE or Acute dietary MOE = Acute aggregate NOAEL of 250 mg/kg bw/day ÷ acute dermal or acute dietary exposure

[4] Aggregate exposure risk (MOE) =MOE_{Total} = 1/ [(1/MOE Acute Dermal) + (1/MOE Acute Dietary)]

Table 9a Integrated Food Residue Chemistry Summary

<table>
<tr><th colspan="6">NATURE OF THE RESIDUE IN APPLES</th><th colspan="4">PMRA # 2146859</th></tr>
<tr><td colspan="2">Radiolabel Position</td><td colspan="8">[^{14}C- t-butylphenyl]-Cyflumetofen and [^{14}C-benzoyl]-Cyflumetofen</td></tr>
<tr><td colspan="2">Test Site</td><td colspan="8">Outdoors</td></tr>
<tr><td colspan="2">Treatment</td><td colspan="8">Foliar spray</td></tr>
<tr><td colspan="2">Rate</td><td colspan="8">600 g a.i./ha</td></tr>
<tr><td colspan="2">End-use product</td><td colspan="8">SC Flowable</td></tr>
<tr><td colspan="2">Preharvest interval</td><td colspan="8">Fruit: 1, 7, and 30 days; Leaves: 7 and 30 days</td></tr>
<tr><td colspan="2" rowspan="2">Matrix</td><td rowspan="2">PHI (days)</td><td colspan="3">[^{14}C- t-butylphenyl]-Cyflumetofen</td><td colspan="4">[^{14}C-benzoyl]-Cyflumetofen</td></tr>
<tr><td>TRR (ppm)</td><td>% TRR Surface Rinse</td><td>% TRR Extractable</td><td>TRR (ppm)</td><td colspan="2">% TRR Surface Rinse</td><td>% TRR Extractable</td></tr>
<tr><td colspan="2">Apple</td><td>1</td><td>0.100</td><td>95.0</td><td>-</td><td>0.113</td><td colspan="2">95.6</td><td>-</td></tr>
<tr><td colspan="2">Apple</td><td>7</td><td>0.078</td><td>82.1</td><td>15.4</td><td>0.167</td><td colspan="2">89.2</td><td>9.6</td></tr>
<tr><td colspan="2">Apple</td><td>30</td><td>0.079</td><td>70.9</td><td>21.5</td><td>0.057</td><td colspan="2">66.7</td><td>28.1</td></tr>
<tr><td colspan="2">Leaves</td><td>7</td><td>6.099</td><td>90.8</td><td>7.9</td><td>7.266</td><td colspan="2">86.8</td><td>11.6</td></tr>
<tr><td colspan="2">Leaves</td><td>30</td><td>4.932</td><td>82.0</td><td>13.0</td><td>9.564</td><td colspan="2">72.0</td><td>21.3</td></tr>
<tr><td colspan="2">Metabolites Identified</td><td colspan="4">Major Metabolites (>10% TRR)</td><td colspan="4">Minor Metabolites (<10% TRR)</td></tr>
<tr><td rowspan="2">Matrix</td><td rowspan="2">PHI, days</td><td colspan="2">[^{14}C- t-butylphenyl]-Cyflumetofen</td><td colspan="2">[^{14}C-benzoyl]-Cyflumetofen</td><td colspan="2">[^{14}C- t-butylphenyl]-Cyflumetofen</td><td colspan="2">[^{14}C-benzoyl]-Cyflumetofen</td></tr>
<tr><td>Surface Rinse</td><td>Extract</td><td>Surface Rinse</td><td>Extract</td><td>Surface Rinse</td><td>Extract</td><td>Surface Rinse</td><td>Extract</td></tr>
<tr><td>Apple</td><td>1</td><td>Cyflumetofen</td><td>-</td><td>Cyflumetofen</td><td>-</td><td>AB-6</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Apple</td><td>7</td><td>Cyflumetofen</td><td>-</td><td>Cyflumetofen</td><td>-</td><td>AB-6</td><td>-</td><td>AB-7, B-1</td><td>AB-7</td></tr>
<tr><td>Apple</td><td>30</td><td>Cyflumetofen</td><td>-</td><td>Cyflumetofen</td><td>Cyflumetofen</td><td>AB-6, AB-7</td><td>AB-6, AB-7, Cyflumetofen</td><td>AB-6, AB-7</td><td>AB-7, AB-6, B-1</td></tr>
<tr><td>Leaves</td><td>7</td><td>Cyflumetofen</td><td>-</td><td>Cyflumetofen</td><td>-</td><td>AB-6, AB-7</td><td>Cyflumetofen, AB-6, AB-7</td><td>AB-6, AB-7, B-1</td><td>Cyflumetofen, AB-6, AB-7, B-1</td></tr>
<tr><td>Leaves</td><td>30</td><td>Cyflumetofen</td><td>-</td><td>Cyflumetofen</td><td>-</td><td>AB-6, AB-7</td><td>Cyflumetofen, AB-6, AB-7</td><td>AB-6, AB-7, B-1</td><td>Cyflumetofen, AB-6, AB-7, B-1</td></tr>
<tr><td colspan="10">Unextractable radioactive residues were 1.2-7.6 % TRRs for all matrices and were not further analyzed.</td></tr>
</table>

Table 9b Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN EGGPLANTS	**PMRA # 2146858**
Radiolabel Position	**[^{14}C- t-butylphenyl]-Cyflumetofen and [^{14}C-benzoyl]-Cyflumetofen**
Test Site	Outdoors
Treatment	Foliar spray
Rate	600 g a.i./ha
End-use product	SC Flowable
Preharvest interval	Fruit: 1, 7, and 14 days; Leaves: 14 days

Matrix	**PHI (days)**	**[^{14}C- t-butylphenyl]-Cyflumetofen**			**[^{14}C-benzoyl]-Cyflumetofen**		
		TRR (ppm)	**% TRR Surface Rinse**	**% TRR Extractable**	**TRR (ppm)**	**% TRR Surface Rinse**	**% TRR Extractable**
Eggplant	1	0.323	92.0	7.1	0.488	86.5	12.7
Eggplant	7	0.375	86.1	11.5	0.558	79.2	19.4
Eggplant	14	0.315	81.3	14.6	0.413	56.4	40.9
Leaves	14	22.968	83.4	14.1	17.463	68.7	26.6

Metabolites Identified		**Major Metabolites (>10% TRR)**				**Minor Metabolites (<10% TRR)**			
Matrix	**PHI, days**	**[^{14}C- t-butylphenyl]-Cyflumetofen**		**[^{14}C-benzoyl]-Cyflumetofen**		**[^{14}C- t-butylphenyl]-Cyflumetofen**		**[^{14}C-benzoyl]-Cyflumetofen**	
		Surface Rinse	Extract	Surface Rinse	Extract	Surface Rinse	Extract	Surface Rinse	Extract
Eggplant	1	Cyflumetofen	-	Cyflumetofen	B-1	-	Cyflumetofen	-	Cyflumetofen, B-1
Eggplant	7	Cyflumetofen	-	Cyflumetofen	-	AB-6, AB-7, U-4	Cyflumetofen	AB-6, AB-7, B-1	Cyflumetofen, B-1, U-2, U-1
Eggplant	14	Cyflumetofen	-	Cyflumetofen	B-1	AB-6, AB-7, U-4	Cyflumetofen	AB-6, AB-7, U-4	Cyflumetofen, B-1, U-2, U-1
Leaves	14	Cyflumetofen	-	Cyflumetofen	-	AB-6, AB-7, U4, U3	Cyflumetofen, AB-6, AB-7	AB-6, AB-7, U-4, U-3, B-1	Cyflumetofen, AB-6, AB-7, B-1, U-4. U-2, U-1
Unextractable radioactive residues were 0.9-4.7 % TRRs for all matrices and were not further analyzed.									

Table 9c Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN MANDARINS	**PMRA # 2146860**
Radiolabel Position	**[^{14}C- t-butylphenyl]-Cyflumetofen and [^{14}C-benzoyl]-Cyflumetofen**
Test Site	Phytotron
Treatment	Foliar spray
Rate	600 g a.i./ha
End-use product	SC Flowable
Preharvest interval	Fruit: 1, 7, and 30 days; Leaves: 1, 7, and 14 days

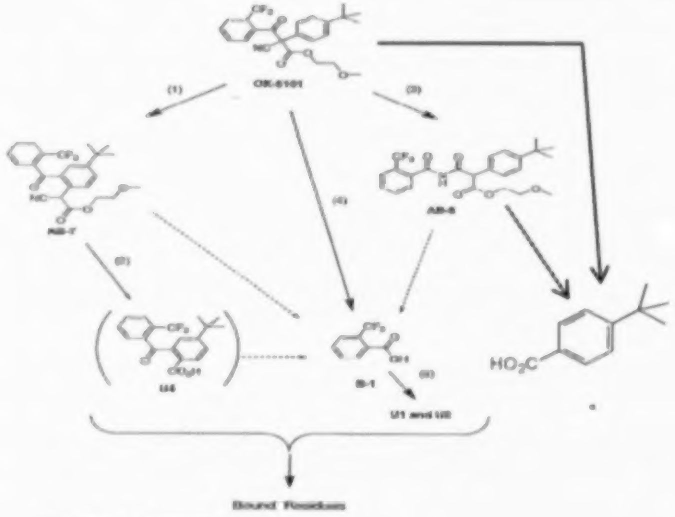
Matrix	**PHI (days)**	**[^{14}C- t-butylphenyl]-Cyflumetofen**			**[^{14}C-benzoyl]-Cyflumetofen**		
		TRR (ppm)	**% TRR Surface Rinse**	**% TRR Peel or leaf Extract**	**TRR (ppm)**	**% TRR Surface Rinse**	**% TRR Peel or leaf Extract**
Mandarin	1	0.578	95.6	3.7	0.617	95.0	4.3
Mandarin	7	0.449	93.0	5.7	0.419	91.4	7.5
Mandarin	30	0.571	88.8	9.1	0.574	87.9	10.1
Leaves	1	36.09	96.6	3.1	35.06	95.1	4.7
Leaves	7	31.54	93.5	5.8	33.75	91.2	8.2
Leaves	14	30.01	94.4	4.9	43.13	87.1	12.4

Metabolites Identified		**Major Metabolites (>10% TRR)**				**Minor Metabolites (<10% TRR)**			
Matrix	**PHI, days**	**[^{14}C- t-butylphenyl]-Cyflumetofen**		**[^{14}C-benzoyl]-Cyflumetofen**		**[^{14}C- t-butylphenyl]-Cyflumetofen**		**[^{14}C-benzoyl]-Cyflumetofen**	
		Surface Rinse	Peel or leaf Extract	Surface Rinse	Peel or leaf Extract	Surface Rinse	Peel or leaf Extract	Surface Rinse	Peel or leaf Extract
Mandarin	1	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, A-12, AB-6, AB-7	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7
Mandarin	7	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, A-12, AB-6, AB-7	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7
Mandarin	30	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, A-12, AB-6, AB-7	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7
Leaves	1	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, AB-6, AB-7, A-12	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7
Leaves	7	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, AB-6, AB-7, A-12	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7
Leaves	14	Cyflumetofen	-	Cyflumetofen	-	A-12, AB-6, AB-7	Cyflumetofen, AB-6, AB-7, A-12	B-1, AB-6, AB-7	Cyflumetofen, B-1, AB-6, AB-7

Unextractable radioactive residues from peel and leaves were <1.4 % TRRs and were not further analyzed. The radioactive residues in mandarin pulp without peel were <0.06 % of the TRR, and were not further analyzed.

Table 9d Integrated Food Residue Chemistry Summary

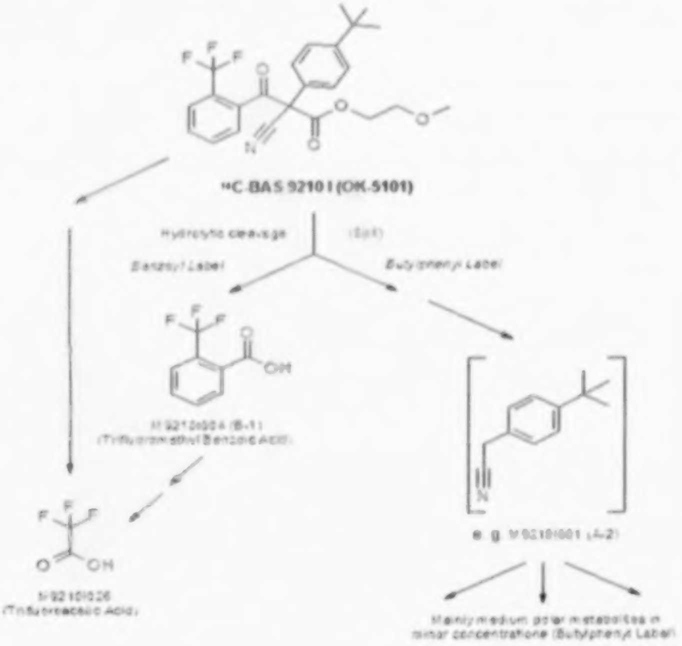
CONFINED ACCUMULATION IN ROTATIONAL CROPS – LETTUCE, WHITE RADISH, and SPRING WHEAT		**PMRA # 2146884**			
Radiolabel Position		**[^{14}C- t-butylphenyl]-Cyflumetofen and [^{14}C-benzoyl]-Cyflumetofen**			
Test site		Phytotrons/Greenhouses			
Formulation used for trial		Aqueous solution prepared with MeOH			
Application rate and timing		400 g a.i./ha applied to bare soil, 30, 120, and 365 days before planting rotational crops			
Metabolites Identified		**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Matrix	**PBI (days)**	**[^{14}C- t-butylphenyl]-Cyflumetofen**	**[^{14}C-benzoyl]-Cyflumetofen**	**[^{14}C- t-butylphenyl]-Cyflumetofen**	**[^{14}C-benzoyl]-Cyflametofen**
Lettuce-Immature, Mature	30 120 365	-	Trifluoro-acetic acid	-	-
White Radish-Root, Top	30 120 365	-	Trifluoro-acetic acid	-	-
Spring Wheat – Forage, Hay, Straw & Chaff, Grain	30 120 365	-	Trifluoro-acetic acid*	-	-**
*Trifluoroacetic acid (TFA) was absent in forage at 365 day PBI. **Traces of the metabolite B-1 in wheat grain at 30 day PBI.					
The confined crop rotation study showed that cyflumetofen was readily degraded in soil to TFA and other medium polar metabolites (accounting for <0.01 ppm) and taken up by rotational crops. TFA is a common metabolite to other pesticides and is also ubiquitous in the environment. Therefore, it is not a feasible marker for cyflumetofen. On this basis, a field accumulation study for rotational crops was not required.					
Proposed Metabolic Pathway in Plants					



(1). Photochemical rearrangement
(2). Hydrolysis/oxidation of side chain
(3). Nitrile hydrolysis to amide, followed by acyl migration.
(4). Hydrolysis.
(5). Conjugation.

CONFINED ACCUMULATION IN ROTATIONAL CROPS – LETTUCE, WHITE RADISH, and SPRING WHEAT	PMRA # 2146884

Proposed Metabolic Pathway in Rotational Crops



F
F
F
O
N
O
O
O
^{14}C-BAS 9210 I (OK-5101)
Hydrolytic cleavage
(Soil)
Benzoyl Label
Butylphenyl Label
F
F
F
O
OH
M 9210I004 (B-1)
(Trifluoromethyl Benzoic Acid)
N
e.g. M 9210I001 (A-2)
F
F
F
O
OH
M 9210I026
(Trifluoroacetic Acid)
Mainly medium polar metabolites in minor concentrations (Butylphenyl Label)

Table 9e Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN LAYING HEN	PMRA # not applicable
A study involving the metabolism of cyflumetofen in the laying hen was not submitted and is not required as the current registration does not involve treatment of crops that would be fed to poultry.	
NATURE OF THE RESIDUE IN LACTATING GOAT	**PMRA # 2146865, 2146863**
Goats were fed [^{14}C- phenyl]-Cyflumetofen and [^{14}C-tolyl]-Cyflumetofen separately, each at a nominal dose of 12 mg a.i./kg feed/day for 10-12 days. Residues were predominantly excreted in urine (~32-42 % administered dose) and feces (~47 % administered dose). While all tissues contained B-1 as a major metabolite, milk contained B-1 as a minor metabolite. Unchanged cyflumetofen was only observed, as a predominant residue, in fat.	

Matrices	% of Administered Dose[1]	
	[^{14}C- t-butylphenyl]-Cyflumetofen	[^{14}C-benzoyl]-Cyflumetofen
Urine	41.855	31.741
Feces	46.460	46.436
Flank Muscle	0.006	0.004
Fat	0.002	0.002
Kidney	0.013	0.017
Liver	0.120	0.169
Milk	0.031	0.121

[1] Average from two goats for each radiolabel.

Metabolites identified	Major Metabolites (>10% TRR)		Minor Metabolites (<10% TRR)	
Radiolabel Position	**[^{14}C- t-butylphenyl]-Cyflumetofen**	**[^{14}C-benzoyl]-Cyflumetofen**	**[^{14}C- t-butylphenyl]-Cyflumetofen**	**[^{14}C-benzoyl]-Cyflumetofen**
Milk	M92101033	-	M92101023, M92101029, M92101030	B-1
Liver	-	B-1	M92101042, M92101043	M92101042
Kidney	M92101023	B-1	M92101033, M92101032, M92101030, A-2, A-12	-
Muscle	-	B-1	-	-
Fat	A-2	Cyflumetofen, B-1	-	-

Proposed Metabolic Pathway in Livestock

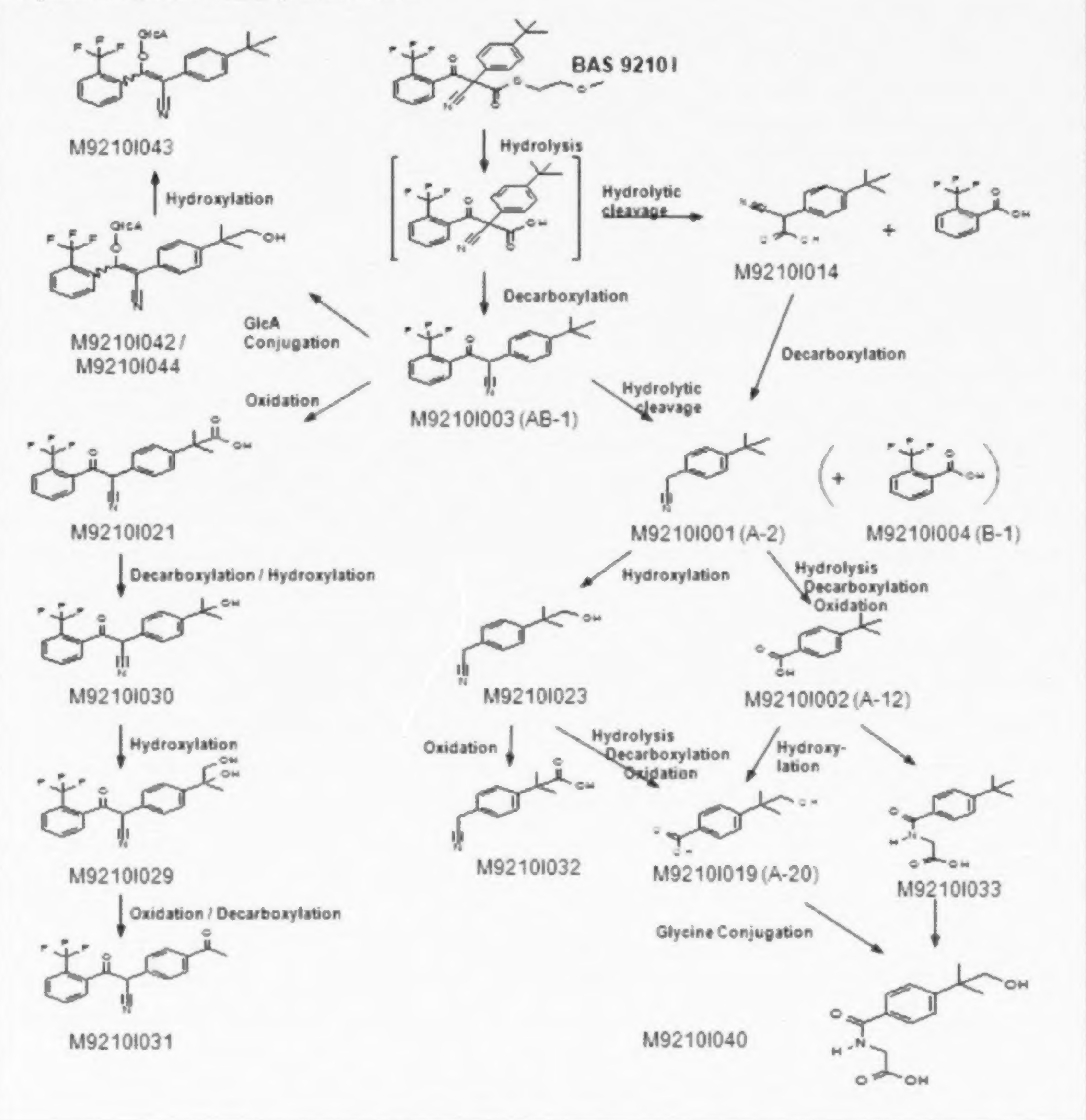

BAS 9210I
Hydrolysis
Hydrolytic cleavage
M9210I014
Decarboxylation
M9210I043
Hydroxylation
GlcA
GlcA Conjugation
M9210I042 / M9210I044
Decarboxylation
Oxidation
M9210I003 (AB-1)
Hydrolytic cleavage
M9210I021
M9210I001 (A-2)
M9210I004 (B-1)
Decarboxylation / Hydroxylation
Hydroxylation
Hydrolysis Decarboxylation Oxidation
M9210I030
M9210I023
M9210I002 (A-12)
Hydroxylation
Oxidation
Hydrolysis Decarboxylation Oxidation
Hydroxy-lation
M9210I029
M9210I032
M9210I019 (A-20)
M9210I033
Oxidation / Decarboxylation
Glycine Conjugation
M9210I031
M9210I040

Table 9f Integrated Food Residue Chemistry Summary

STORAGE STABILITY **PMRA # 2292026**

The storage stability of cyflumetofen and metabolites B-1, AB-6, and AB-7 at -10°C was studied for 24-30 months at individual spiking levels of 0.1 ppm. Specifically, stability in almond nutmeat (high oil), apple fruit (high water), apple juice, kidney bean dried seed (high protein), leaf lettuce leaves (high water), orange whole fruit (high acid), orange juice, orange oil, radish root (high starch), and wheat grain (high starch) was examined.

The results indicate that parent cyflumetofen is stable for 24 months with the following two exceptions. In kidney bean, recovery was 65 % after 18 months, and decreased to 39 % after 25 months of frozen storage. In leaf lettuce, recovery was 65 % after 11 months, and decreased to 54 % after 28 months of frozen storage. As a result, some correction factors were required to account for potential losses during frozen storage.

As measurable residues in animal commodities are not anticipated, a freezer storage stability study for animal matrices is not required for the purpose of this submission.

RESIDUE STUDIES

As part of the NAFTA Joint Review, crop trials from the NAFTA representative growing regions for Citrus Fruit (CG 10-revised), Pome Fruits (CG 11-09), Tree Nuts (CG 14-11), strawberry, tomato, and grapes were submitted.

For residue decline trials, residues of cyflumetofen generally declined with increasing PHI.

CITRUS FRUITS, CG 10-revised (US GAP: 448 g a.i./ha, 7 day PHI) **PMRA # 2199469**

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Oranges	398-411	7	24	0.010	0.159	0.116	0.074	0.070	0.037
Grapefruit	400-408	7	12	<0.010	0.077	0.072	0.037	0.037	0.020
Lemons	391-402	7	10	<0.010	0.141	0.135	0.021	0.054	0.051

POME FRUITS, CG 11-09 (CDN GAP: 400 g a.i./ha, 7 day PHI) **PMRA # 2146869**

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Apples	391-420	6-8	48	<0.010	0.248	0.199	0.078	0.092	0.060
Pears	396-415	7-8	20	0.032	0.265	0.193	0.098	0.098	0.052

TREE NUTS, CG 14-11 (US GAP: 448 g a.i./ha, 7 day PHI) **PMRA # 2146021**

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Almond nutmeat	397-400	7	10	<0.010	<0.010	<0.010	0.010	0.010	0
Pecan nutmeat	393-409	7-8	16	<0.010	<0.010	<0.010	0.010	0.010	0

GRAPES (CDN GAP: 400 g a.i./ha, 14 day PHI) **PMRA # 2146877**

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Grapes	392-404	14	24	0.014	0.439	0.422	0.152	0.175	0.103

STRAWBERRY (CDN GAP: 400 g a.i./ha, 1 day PHI) **PMRA # 2146874**

Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Strawberry	393-405	1	16	0.038	0.437	0.365	0.155	0.171	0.100

TOMATO (CDN GAP: 400 g a.i./ha, 3 day PHI)									**PMRA # 2146875**
Commodity	Total Appl. Rate (g a.i./ha)	PHI (days)	Residues (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Tomato	386-408	3	32	<0.019	0.298	0.274	0.075	0.097	0.070

Table 9g Integrated Food Residue Chemistry Summary

FIELD ACCUMULATION IN ROTATIONAL CROPS	**PMRA # not applicable**
A field accumulation study for cyflumetofen in rotational crops was not submitted and is not required on the basis of the results from the confined crop rotation study. This study showed that cyflumetofen was readily degraded in soil to TFA and other medium polar metabolites (accounting for <0.01 ppm) and taken up by rotational crops. TFA is a common metabolite to other pesticides and is also ubiquitous in the environment. Therefore, it is not a feasible marker for cyflumetofen. On this basis, a field accumulation study for rotational crops was not required.	
PROCESSED FOOD AND FEED	**PMRA # 2146871, 2146022, 2146879, 2146883**
RAC	**Processed Fraction***
Citrus (orange)	Wet pomace (0.2X) **Peel (3.0X)** Dried pulp (0.5X) Juice (0.05X) **Oil (119X)** Meal (0.4X) Molasses (<0.1X) Marmalade (0.1X)
Apple	**Wet pomace (1.3X)** **Apple sauce (2.7X)** Juice (0.25X) Dried fruit (0.5X) Canned fruit (0.1X)
Tomato	Washed fruit (0.9X) Peeled fruit (0.1X) Canned fruit (0.1X) Puree (0.6X) Paste (0.3X) **Wet pomace (3.4X)** **Peels (13X)** **Wash water (1.5X)** Juice (0.15X)
Grape	**Raisin (1.4X)** **Raisin stem (9.8X)** **Pomace (3.2X)** **Yeast (4.0X)** **Grape stems (2.5X)** Juice (0.15X) Young Wine (<0.1X) Must (0.3X)
*Commodities in bold indicate processing factors of >1X, or concentration of residues.	

Table 9h Integrated Food Residue Chemistry Summary

<table>
<tr><th colspan="3">LIVESTOCK FEEDING – Dairy cattle & Laying hen</th><th colspan="2">PMRA # 2146882 (waiver)</th></tr>
<tr><td colspan="5">The petitioner provided a waiver for livestock dairy cattle feeding study on the basis that wet apple pomace is the only potential feed item for ruminants, and that the goat metabolism study can be used to estimate the level of exposure for ruminants. The PMRA accepts this approach, and the goat metabolism study is accepted in <i>lieu</i> of a cattle feeding study.

Furthermore, the petitioner provided a waiver for a laying hen feeding study on the basis that there are no feed items for poultry in this submission. The PMRA agrees with this approach, and a laying hen feeding study is not required at this time.</td></tr>
<tr><td colspan="5">The following is a projection of anticipated residues from the goat metabolism study (PMRA #'s 2146863, 2146865) for ruminants.</td></tr>
<tr><td>Commodity</td><td>Feeding level (ppm)</td><td>Residue in Tissue (ppm)*</td><td>Dietary Burden (ppm)</td><td>Anticipated Residues (ppm)</td></tr>
<tr><td>Milk</td><td>13.5</td><td>0.019</td><td>0.030</td><td>0.000042</td></tr>
<tr><td>Fat (cattle)</td><td>13.5</td><td>0.010</td><td>0.030</td><td>0.000031</td></tr>
<tr><td>Kidney (cattle)</td><td>13.5</td><td>0.014</td><td>0.030</td><td>0.00042</td></tr>
<tr><td>Liver (cattle)</td><td>13.5</td><td>0.404</td><td>0.030</td><td>0.00090</td></tr>
<tr><td>Muscle (cattle)</td><td>13.5</td><td>0.191</td><td>0.030</td><td>0.000022</td></tr>
<tr><td colspan="5">*These values correspond to the TRRs from the goat metabolism study where the benzoyl label was administered. The results for benzoyl label were used since it yielded greater transfer of residues to tissue and milk as compared to those from the t-butylphenyl label.</td></tr>
</table>

Table 10 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

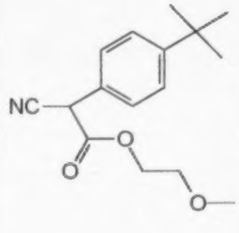
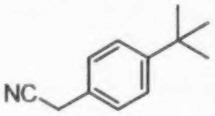
<table>
<tr><th colspan="4">PLANT STUDIES</th></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT
Primary crops
Rotational crops</td><td colspan="2">Cyflumetofen
-</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT
Primary crops
Rotational crops</td><td colspan="2">Cyflumetofen
-</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN DIVERSE CROPS</td><td colspan="2">The metabolic profile of cyflumetofen in mandarin, eggplant, and apples is understood.</td></tr>
<tr><th colspan="4">ANIMAL STUDIES</th></tr>
<tr><td colspan="2">ANIMALS</td><td colspan="2">Ruminant</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT</td><td colspan="2">Cyflumetofen and B-1</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT</td><td colspan="2">Cyflumetofen and B-1</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN ANIMALS
(goat, rat)</td><td colspan="2">The metabolic profile in ruminants is understood and is the same as the rat.</td></tr>
<tr><td colspan="2">FAT SOLUBLE RESIDUE</td><td colspan="2">Yes</td></tr>
<tr><td colspan="4">DIETARY RISK FROM FOOD AND WATER</td></tr>
<tr><td rowspan="7">Refined chronic non-cancer dietary risk

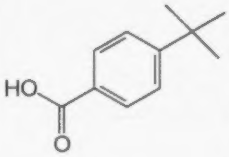
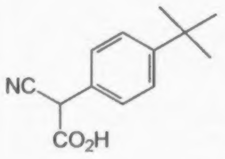
ADI = 0.2 mg/kg bw

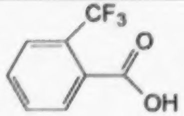
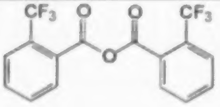
Estimated chronic drinking water concentration = 12 μg/L</td><td rowspan="2">POPULATION</td><td colspan="2">ESTIMATED RISK
% of ACCEPTABLE DAILY INTAKE (ADI)</td></tr>
<tr><td>Food Only</td><td>Food and Water</td></tr>
<tr><td>All infants <1 year</td><td>2.7</td><td>3.2</td></tr>
<tr><td>Children 1–2 years</td><td>6.1</td><td>6.3</td></tr>
<tr><td>Children 3 to 5 years</td><td>4.3</td><td>4.5</td></tr>
<tr><td>Children 6–12 years</td><td>2.2</td><td>2.3</td></tr>
<tr><td>Youth 13–19 years</td><td>1.2</td><td>1.3</td></tr>
</table>

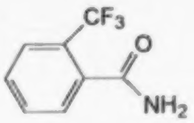
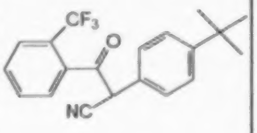
	Adults 20–49 years	0.9	1.1
	Adults 50+ years	0.9	1.1
	Females 13-49 years	1.0	1.1
	Total population	1.4	1.6
Refined acute dietary exposure analysis, 95th percentile **Estimated acute drinking water concentration = 20 μg/L**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
ARfD = 0.8 mg/kg bw	**Females 13–49 years**	0.71	0.75

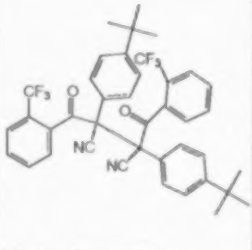
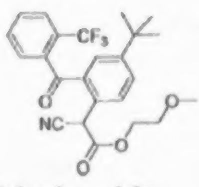
Table 11 Summary of Formation of Major[1] Transformation Products and Volatile Compounds [(Maximum %AR and Sampling Interval, Days After Treatment (DAT)] in Cyflumetofen Laboratory Studies

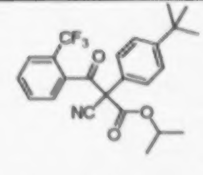
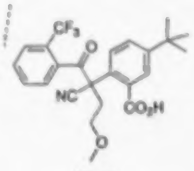
Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
A-1 2-methoxyethyl (RS)-(4-tert-butylphenyl) (cyano) acetate	 Molecular weight: 275.35	Hydrolysis **[2146729]**	**pH 4:** 26.94% (21 d) **pH 5:** 10.02% (7 d) **pH 7:** 14.44% (8 hr) **pH 9:** 28.27% (15 min)
		Aquatic photolysis **[2146732]**	***pH 5 buffer*** irradiated: 2.71% (2 d) dark: ND[2] ***pH 7.48 natural water*** irradiated: 6.02% (1 hr) dark: 17.82 (4 hr)
		Aerobic soil biotransformation **[2146891]**	New Jersey soil: ***(A-1 dimer)*** 2.3% (29 d)
		Anaerobic soil biotransformation **[2146893]**	New Jersey soil: ***(A-1 + A-2 combined)*** water phase: 1.3% (3 d) soil phase: 1.1% (3 d)
A-2 (4-tert-butylphenyl) acetonitrile	 Molecular weight: 173.26	Hydrolysis **[2146729]**	**pH 4:** 14.55% (30 d) **pH 5:** 14.12% (21 d) **pH 7:** 19.22% (120 hr) **pH 9:** 15.05% (90 min)
		Aquatic photolysis **[2146732]**	***pH 5 buffer*** irradiated: 2.14% (2 d) dark: 0.48% (2 d) ***pH 7.48 natural water*** irradiated: 3.16% (2 d) dark: 15.56% (2 d)
		Aerobic soil biotransformation **[2146891]**	New Jersey soil: 2.6% (29 d)
		Anaerobic soil biotransformation **[2146893]**	New Jersey soil: ***(A-1 + A-2 combined)*** water phase: 1.3% (3 d) soil phase: 1.1% (3 d)

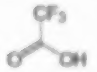
Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
		Aerobic water/sediment biotransformation **[2146936]** **Netherlands systems**	**System** **Water phase** **Sediment phase** GV A-ring 9.3% (15 d) 2.7% (15 d) SW A-ring 18.4% (0.7 d) 6.1% (57 d)
		Anaerobic water/sediment biotransformation **[2146934]** **U.S. systems**	**System** **Water phase** **Sediment phase** Penn. A-ring 19.49% (3 d) 17.39% (90 d) Fld. A-ring 14.17% (15 d) 40.49% (90 d)
A-12 4-tert-butylbenzoic acid	 Molecular weight: 178.23	Aquatic photolysis **[2146732]**	***pH 5 buffer*** irradiated: 3.77% (2 d) dark: ND ***pH 7.48 natural water*** irradiated: 18.25% (2 d) dark: 2.06% (2 d)
		Aerobic soil biotransformation **[2146891]**	New Jersey soil: 7.1% (29 d)
		Anaerobic soil biotransformation **[2146893]**	New Jersey soil: water phase: 8.4% (120 d) soil phase: 1.4% (120 d)
		Aerobic water/sediment biotransformation **[2146932** **U.S. systems**	**System** **Water phase** **Sediment phase** Penn. A-ring 4.5% (8 d ND (133 d) Fld. A-ring 17.6% (15 d) ND (133 d)
		Anaerobic water/sediment biotransformation **[2146934]** **U.S. systems**	**System** **Water phase** **Sediment phase** Penn. A-ring 29.46% (15 d) 8.62% (90 d) Florida A-ring 6.31% (30 d) 2.83% (90 d)
A-18	 Molecular weight: 217.27	Hydrolysis **[2146729]**	**pH 4:** 12.63% (30 d) **pH 5:** 8.63% (21 d) **pH 7:** 36.22% (120 hr) **pH 9:** 48.80% (1440 min)
		Aquatic photolysis **[2146732]**	***pH 5 buffer*** irradiated: 0.99% (2 d) dark: ND ***pH 7.48 natural water*** irradiated: 3.82% (4 hr) dark: 26.84% (2 d)
B-1 2-(trifluoromethyl)		Hydrolysis **[2146729]**	**pH 4:** 48.40% (30 d) **pH 5:** 52.62% (30 d) **pH 7:** 52.85% (240 hr) **pH 9:** 50.31% (1440 min)

Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
benzoic acid	 Molecular weight: 190.12	Aquatic photolysis **[2146732]**	***pH 5 buffer*** irradiated: 11.88% (2 d) dark: 13.27% (2 d) ***pH 7.48 natural water*** irradiated: 40.13% (2 d) dark: 51.53% (2 d)
		Soil photolysis **[2146897]**	German soil irradiated: 47.6% (5.8 d) dark: 37.7% (13.8 d)
		Aerobic soil biotransformation **[2146899]** **U.K. soil** **[2146891]** **U.S. soils** **[2146900]** **German soils**	Wolston soil: 22.9% (6 d) NJ soil: 30.9% (16 d) CA soil: 43.8% (58 d) IN soil: 24.0% (7 d) WI soil: 21.0% (7 d) Speyer 2.2 soil: 63.0% (90 d) Speyer 2.3 soil: 43.2% (35 d) Speyer 6S soil: 52.8% (58 d)
		Anaerobic soil biotransformation **[2146893]** **U.S. soils**	**Soil Water phase Soil phase** NJ 48.2% (120 d) 20.5% (3 d) CA 45.6% (120 d) 21.7% (3 d) IN 45.7% (120 d) 15.7% (3 d) WI 40.3% (120 d) 11.8% (3 d)
		Aerobic water/sediment biotransformation **[2146932]** **U.S. systems** **[2146939]** **Netherlands systems**	**System Water phase Sediment phase** Penn. B-ring 53.1% (59 d) 8.5% (100 d) Fld. B-ring 46.5% (30 d) 15.0% (133 d) GV B-ring 50.9% (62 d) 9.9% (103 d) SW B-ring 65.0% (5 d) 21.5% (29 d)
		Anaerobic water/sediment biotransformation **[2146934]** **U.S. systems**	**System Water phase Sediment phase** Penn. B-ring 56.97% (120 d) 13.15% (90 d) Fld. B-ring 54.80% (120 d) 14.59% (90 d)
B-2 α,α,α-trifluoro-o-toluic anhydride	 Molecular weight: 394.31	Aerobic water/sediment biotransformation **[2146939]** **Netherlands systems**	**System Water phase Sediment phase** GV B-ring ND (103 d) 28.0% (2 d) SW B-ring 15.4% (0.7 d) 10.9% (12 d)

Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
B-3 2-(trifluoromethyl) benzamide	 Molecular weight: 189.14	Aerobic soil biotransformation **[2146891** **U.S. soils** **[2146900** **German soils**	NJ soil: 5.0% (7 d) CA soil: 18.0% (16 d) IN soil: 4.6% (7 d) WI soil: 3.2% (16 d) Speyer 2.2 soil: 23.0% (21 d) Speyer 2.3 soil: 12.7% (6 d) Speyer 6S soil: 4.8% (21 d)
		Anaerobic soil biotransformation **[2146893]** **U.S. soils**	System Water phase Sediment phase NJ 1.1% (30 d) ND (120 d) CA 2.9% (30 d) ND (120 d) IN 3.0% (15 d) ND (120 d) WI 1.3% (30 d) ND (120 d)
AB-1 (RS)-2-(4-tert-butylphenyl)-3-oxo-3-[2-(trifluoromethyl) phenyl] propanenitrile	 Molecular weight: 345.37	Hydrolysis **[2146729]**	**pH 4** A-ring: 34.80% (30 d) B-ring: 34.17% (30 d) **pH 5** A-ring: 19.93% (30 d) B-ring: 23.35 % (30 d) **pH 7** A-ring: 44.51% (120 hr) B-ring: 41.18% (240 hr) **pH 9** A-ring: 44.75% (1440 min) B-ring: 45.68% (1440 min)
		Aquatic photolysis **[2146732]**	**pH 5 buffer** A-ring irradiated: 2.37% (2 d) dark: 4.67% (2 d) B-ring irradiated: 2.37% (2 d) dark: 6.37% (2 d) **pH 7.48 natural water** A-ring irradiated: 12.45% (4 hr) dark: 43.36% (2 d) B-ring irradiated: 12.27 (4 hr) dark: 43.77% (2 d)
		Soil photolysis **[2146895]** **German soil** **[2146897]** **German soil**	A-ring irradiated: <5% (14.7 d) dark: <5% (14.7 d) B-ring irradiated: <5% (13.8 d) dark: <5% (13.8 d)
		Aerobic soil biotransformation **[2146899]** **U.K. soil** **[2146891]** **U.S. soils**	Wolston soil A-ring: 8.3% (59 d) Wolston soil B-ring: 7.8% (30 d) NJ soil A-ring: 17.7% (7 d) NJ soil B-ring: 7.2% (58 d) CA soil B-ring: 6.8% (29 d) IN soil B-ring: 6.2% (58 d) WI soil B-ring: 11.1% (16 d)

Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
		Anaerobic soil biotransformation **[2146893]** **U.S. soils**	**Soil Water phase Soil phase** NJ A-ring 7.9% (120 d) 19.3% (30 d) NJ B-ring 5.1% (30 d) 20.2% (7 d) CA B-ring 8.4% (58 d) 13.9% (15 d) IN B-ring 4.7% (30 d) 16.1% (7 d) WI B-ring 10.4% (58 d) 26.9% (15 d)
		Aerobic water/sediment biotransformation **[2146932]** **U.S. systems** **[2146936]** **Netherlands systems**	**System Water phase Sediment phase** Penn. A-ring 2.8% (0 d) 3.8% (59, 133 d) Penn. B-ring 4.2% (1 d) 7.0% (100 d) Fld. A-ring 3.3% (0 d) 8.5% (133 d) Fld. B-ring 8.2% (4 d) 10.5% (133 d) GV A-ring 2.0% (15 d) 4.6% (15 d) SW A-ring 6.4% (0.7 d) 14.6% (29 d)
		Anaerobic water/sediment biotransformation **[2146934]** **U.S. systems**	**System Water phase Sediment phase** Penn. A-ring 21.93% (15 d) 15.14% (30 d) Penn. B-ring 25.28% (30 d) 12.59% (120 d) Fld. A-ring 6.92% (90 d) 25.10% (120 d) Fld. B-ring 7.67% (120 d) 17.27% (120 d)
AB-1 dimer	 Molecular weight: 690.73	Aerobic soil biotransformation **[2146891]** **U.S. soils**	NJ soil A-ring: 18.7% (7 d) NJ soil B-ring: 25.4% (120 d) CA soil B-ring: 18.7% (120 d) IN soil B-ring: 23.5% (7 d) WI soil B-ring: 23.0% (120 d)
		Anaerobic soil biotransformation **[2146893]** **U.S. soils**	**(AB-1 dimer 1 + AB-1dimer 2)** **Soil Water phase Soil phase** NJ A-ring 3.1% (58 d) 11.8% (3 d) NJ B-ring 2.6% (58 d) 14.9% (3 d) CA B-ring 1.9% (58 d) 15.5% (3 d) IN B-ring 1.1% (7 d) 12.3% (3 d) WI B-ring 0.5% (7 d) 12.0% (3 d)
		Aerobic water/sediment biotransformation **[2146932]** **U.S. systems**	**(AB-1 dimer 1 + AB-1dimer 2)** **System Water phase Sediment phase** Penn. A-ring 1.1% (8 d) 5.05 (133 d) Penn. B-ring 0.8% (2 d) 6.8% (133 d) Fld. A-ring 1.7% (15 d) 5.5% (30 d) Fld. B-ring 0.9% (1 d) 7.7% (30 d)
AB-7	 Molecular weight: 447.46	Aquatic photolysis **[2146732]**	**pH 5 buffer** A-ring irradiated: 10.82% (4 hr) dark: 0.66% (2 d) B-ring irradiated: 9.98% (4 hr) dark: 0.75% (2 d) **pH 7.48 natural water** A-ring irradiated: 5.65% (4 hr) dark: 0.65% (4 hr) B-ring irradiated: 5.48% (4 hr) dark: 0.74% (2 d)

Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
AB-11	 Molecular weight: 431.50	Aerobic water/sediment biotransformation **[2146936] Netherlands systems**	SW system, A-ring: water phase: 10.0% (0.7 d) sediment phase: 10.1% (12 d)
AB-15	 AB-15 Molecular weight: 447.46	Aquatic photolysis **[2146732]**	**pH 5 buffer** A-ring irradiated: 53.68% (2 d) dark: 0.90% (1 hr) B-ring irradiated: 54.67% (2 d) dark: ND **pH 7.48 natural water** A-ring irradiated: 37.11% (4 hr) dark: 2.02% (2 d) B-ring irradiated: 34.49% (4 hr) dark: ND
AU-16	**(A-2+AB-1) dimer** Molecular weight: 548.69	Hydrolysis **[2146729]**	**pH 4:** 6.56% (14 d) **pH 5:** 15.78% (30 d) **pH 7:** 5.03% (720 hr) **pH 9:** 4.16% (90 min)
AU-17	**(A-1+AB-1) dimer** Molecular weight: 619.71	Hydrolysis **[2146729]**	**pH 4:** 6.56% (14 d) **pH 5:** 15.78% (30 d) **pH 7:** 5.03% (720 hr) **pH 9:** 4.16% (90 min)
CO_2	O=C=O Molecular weight: 44.01	Soil photolysis **[2146895] German soil** **[2146897] German soil**	A-ring irradiated: 2.5% (14.7 d) dark: 0.5% (14.7 d) B-ring irradiated: 0.3% (13.8 d) dark: ND
		Aerobic soil biotransformation **[2146899] U.K. soil** **[2146891] U.S. soils** **[2146900] German soils**	Wolston A-ring 27.9% (181 d) Wolston B-ring 39.3% (181 d) NJ A-ring 17.3% (120 d) NJ B-ring 24.1% (120 d) CA B-ring 9.9% (120 d) IN B-ring 17.6% (120 d) WI B-ring 17.3% (120 d) Speyer 2.2 B-ring 9.5% (120 d) Speyer 2.3 B-ring 20.7% (120 d) Speyer 6S B-ring 1.7% (120 d)

Code name and Chemical name	Structure and Molecular weight (g/mol)	Study [PMRA number]	Maximum % applied radioactivity (min/hr/day after treatment)
		Anaerobic soil biotransformation **[2146893]** **U.S. soils**	NJ soil A-ring 2.6% (120 d) NJ soil B-ring 1.0% (120 d) CA soil B-ring 0.8% (120 d) IN soil B-ring 1.0% (120 d) WI soil B-ring 1.0% (120 d)
		Aerobic water/sediment biotransformation **[2146932]** **U.S. systems**	Penn. A-ring 8.3% (133 d) Penn. B-ring 3.3% (133 d) Florida A-ring 8.3% (133 d) Florida B-ring 3.0% (133 d)
		[2146936] **Netherlands systems**	GV A-ring 19.9% (98 d) SW A-ring 1.8% (57 d)
		[2146939] **Netherlands systems**	GV B-ring 2.8% (103 d) SW B-ring 3.2% (103 d)
		Anaerobic water/sediment biotransformation **[2146934]** **U.S. systems**	Penn. A-ring 1.53% (120 d) Penn. B-ring 0.16% (120 d) Florida A-ring 0.53% (120 d) Florida B-ring 0.06% (120 d)
Trifluoroacetic acid (TFA)	 Molecular weight: 114.02 Log Kow: 0.79	Acrobic soil biotransformation **[2146891]** **U.S. soils**	Trace amounts detected in the volatile traps
		Aerobic water/sediment biotransformation **[2146932]** **U.S. systems**	Trace amounts detected in the volatile traps

1 Major is defined as greater than 10% of the applied radioactivity.

2 ND: Not detected.

Table 12 Fate and Behaviour of Cyflumetofen and Its Transformation Products in the Terrestrial and Aquatic Environment

Study	Test substance	Study conditions	Results / Values	Comments	PMRA Reference
			Abiotic transformation		
Hydrolysis	Cyflumetofen ^{14}C-A-ring and ^{14}C-B-ring	Buffer solutions pH 4, 5, 7, and 9 25°C	Half-lives (all SFO) at: pH 4: 7.7 d DT$_{90}$: 25.6 d pH 5: 6.0 d DT$_{90}$: 20.0 d pH 7: 9.8 hr DT$_{90}$: 32.6 hr pH 9: 10.3 min DT$_{90}$: 34.2 min	Important route of transformation, especially in alkaline environments	2146729
Photolysis in soil	^{14}C-A-ring Cyflumetofen	**German loam soil** pH 7.2, 2.17% OC, 20°C	Light DT$_{50}$: 2.10 d (SFO) DT$_{90}$: 6.98 d Dark DT$_{50}$: 2.06 d (SFO) DT$_{90}$: 6.85 d	Not expected to play a role in the overall fate of cyflumetofen in soil.	2146895
	^{14}C-B-ring Cyflumetofen	**German loam soil** pH 7.2, 2.17% OC, 20°C	Light DT$_{50}$: 1.4 d (SFO) DT$_{90}$: 4.8 d Dark DT$_{50}$: 1.4 d (SFO) DT$_{90}$: 4.6 d		2146897

Study	Test substance	Study conditions	Results / Values	Comments	PMRA Reference
Photolysis in water	Cyflumetofen ^{14}C-A-ring and ^{14}C-B-ring	**pH 5 sterile buffer** 25℃ (combined labels)	Light DT_{50}: 1.28 hr (SFO) DT_{90}: 4.26 hr Dark DT_{50}: 134.5 hr (SFO) DT_{90}: 446.7 hr **DT_{50} corrected for hydrolysis: 1.24 d**	Could be an important route of transformation in the photic zone of aquatic systems.	2146732
		pH 7.48 sterile natural river water 25℃ (combined labels)	Light DT_{50}: 1.07 hr (SFO) DT_{90}: 3.55 hr Dark DT_{50}: 3.40 hr (SFO) DT_{90}: 11.30 hr **DT_{50} corrected for hydrolysis: 1.20 hr**		
Biotransformation					
Biotrans-formation in aerobic soil	Cyflumetofen ^{14}C-A-ring (NJ soil only) and ^{14}C-B-ring (all soils)	**U.S. soils** **California loamy sand** pH 8.1, 0.28% OC	Cyflumetofen DT_{50}: 3.51 d (IORE) DT_{90}: 16.6 d Representative t½: 4.94 d B-3 DT_{50}: 29.5 d (SFO) DT_{90}: 97.9 d	Cyflumetofen: Non-persistent B-1: Slightly persistent B-3: Slightly persistent	2146891
		Indiana loam pH 6.5, 1.33% OC	Cyflumetofen DT_{50}: 2.28 d (SFO) DT_{90}: 7.56 d		
		New Jersey loam pH 6.9, 1.33% OC	Cyflumetofen (combined labels) DT_{50}: 2.36 d (SFO) DT_{90}: 7.85 d B-1 DT_{50}: 26.4 d (SFO) DT_{90}: 87.8 d		
		Wisconsin loamy sand pH 6.3, 1.57% OC	Cyflumetofen DT_{50}: 3.41 d (SFO) DT_{90}: 11.3 d B-1 DT_{50}: 17.1 d (SFO) DT_{90}: 56.9 d		
	Cyflumetofen ^{14}C-A-ring and ^{14}C-B-ring	**U.K. sandy loam soil** pH 6.5, 1.9% OC (combined labels)	DT_{50}: 2.76 d (SFO) DT_{90}: 9.16 d	Non-persistent	2146888
	Cyflumetofen ^{14}C-B-ring	**German soils** ***Speyer 2.2* loamy sand** pH 5.6, 2.36% OC	DT_{50}: 4.37 d (SFO) DT_{90}: 14.5 d	Non-persistent	2146900
		Speyer 2.3 sandy loam pH 6.2, 1.02% OC	DT_{50}: 2.79 d (IORE) DT_{90}: 44.3 d Representative t½: 13.3 d		
		Speyer 6S clay pH 7.0, 1.89% OC	DT_{50}: 2.53 d (SFO) DT_{90}: 8.42 d		
	B-1 not radiolabelled	**German soils** **Speyer 2.2 loamy sand** pH 5.4, 2.29% OC	DT_{50}: 6.3 d (SFO) DT_{90}: 21.0 d	Non-persistent to slightly persistent	2146906
		Speyer 2.3 sandy loam pH 6.2, 0.99% OC	DT_{50}: 16.7 d (SFO) DT_{90}: 55.5 d		
		Speyer 6S clay pH 7.2, 1.79% OC	DT_{50}: 36.3 d (SFO) DT_{90}: 121 d		

Study	Test substance	Study conditions	Results / Values	Comments	PMRA Reference
	AB-1 not radiolabelled	**German soils** **Speyer 2.1 sand** pH 5.1, 0.88% OC **Speyer 2.2 loamy sand** pH 5.4, 2.29% OC **Speyer 6S clay** pH 7.2, 1.79% OC	DT_{50}: 0.00002 d (IORE) DT_{90}: 119 d Representative t½: 35.9 d DT_{50}: 0.0004 d (IORE) DT_{90}: 45.3 d Representative t½: 13.6 d DT_{50}: 0.02 d (IORE) DT_{90}: 4.24 d Representative t½: 1.28 d	Non-persistent	2146902
	B-3 not radiolabelled	**German soils** **Speyer 2.2 loamy sand** pH 5.4, 2.29% OC **Speyer 2.3 sandy loam** pH 6.2, 0.99% OC **Speyer 6S clay** pH 7.2, 1.79% OC	DT_{50}: 15.1 d (SFO) DT_{90}: 50.1 d DT_{50}: 11.0 d (SFO) DT_{90}: 36.5 d DT_{50}: 12.7 d (SFO) DT_{90}: 42.2 d	Non-persistent to slightly persistent	2146904
Bio-transformation in anaerobic soil	Cyflumetofen ^{14}C-A-ring (NJ soil only) and ^{14}C-B-ring (all soils)	**California loamy sand** pH 8.1, 0.28% OC **Indiana loam** pH 6.5, 1.33% OC **Wisconsin loamy sand** pH 6.3, 1.57% OC **New Jersey loam** pH 6.9, 1.33% OC (combined labels)	DT_{50}: 1.65 d (IORE) DT_{90}: 35.24 d Representative t½: 10.4 d DT_{50}: 0.44 d (IORE) DT_{90}: 6.01 d Representative t½: 1.78 d DT_{50}: 2.14 d (IORE) DT_{90}: 16.43 d Representative t½: 4.88 d DT_{50}: 0.97 d (IORE) DT_{90}: 10.97 d Representative t½: 2.26 d	Non-persistent	2146893
Mobility					
Adsorption/ desorption in soil	Cyflumetofen	Mean value determined by HPLC method according to the OECD Guideline 121	Koc (mL/g): 131826	Immobile	2146911
	B-1	**German soils** **Speyer 2.2 loamy sand** pH 5.7, 2.29% OC **Speyer 2.3 sandy loam** pH 6.3, 1.02% OC **Speyer 6S clay** pH 6.9, 1.90% OC	Mean Koc (mL/g): 112 Mean Koc (mL/g): 3.9 Mean Koc (mL/g): 14.5	Very highly mobile	2146920

Study	Test substance	Study conditions	Results / Values	Comments	PMRA Reference
	AB-1	**German soils** **Speyer 2.2 loamy sand** pH 5.7, 2.29% OC	Mean Koc (mL/g): 65500	Slightly mobile to immobile	2146922
		Speyer 2.3 sandy loam pH 6.3, 1.02% OC	Mean Koc (mL/g): 450000		
		Speyer 6S clay pH 6.9, 1.90% OC	Mean Koc (mL/g): 6200		
	B-3	**German soils** **Speyer 2.2 loamy sand** pH 5.6, 2.36% OC	Mean Koc (mL/g): 11.7	Very highly mobile	2146913
		Speyer 2.3 sandy loam pH 6.3, 1.02% OC	Mean Koc (mL/g): 16.9		
		Speyer 6S clay pH 7.0, 1.89% OC	Mean Koc (mL/g): 12.2		
	A-2 **B-1** **B-3**	Four U.S. and two Europe soils	***A-2*** Mean Kfoc (mL/g): 734 ***B-1*** Mean Kfoc (mL/g): 2.96 ***B-3*** Mean Kfoc (mL/g): 20.37	A-2: Low to moderate B-1 and B-3: Very highly mobile	2146916
	AB-1 dimer	Four U.S. and one German soils	Mean Koc (mL/g): 269800	Immobile	2146918
Soil column leaching	**B-1**	**German soils** **Speyer 2.2 loamy sand** pH 5.4, 2.16% OC	Mean Koc (mL/g): 4.23	Very highly mobile	2146924
		Speyer 2.3 sandy loam pH 6.4, 0.98% OC	Mean Koc (mL/g): 6.56		
		German soil **Speyer 5M sandy loam** pH 7.2, 1.23% OC	Mean Koc (mL/g): 3.70	Very highly mobile	2146926
Aerobic bio-transformation in water/ sediment system	Cyflumetofen ^{14}C-A-ring and ^{14}C-B-ring	**Florida system** pH 5.9 (sed.)/5.9 (water), 2.7% OC	Cyflumetofen (combined labels) DT_{50}: 3.01 d (IORE) DT_{90}: 101 d Representative t½: 30.5 d B-1 DT_{50}: 110 d (SFO) DT_{90}: 366 d	Cyflumetofen: Non-persistent B-1: Moderately persistent	2146932
		Pennsylvania system pH 5.2 (sed.)/7.2 (water), 2.4% OC	Cyflumetofen (combined labels) DT_{50}: 5.53 d (IORE) DT_{90}: 60.6 d Representative t½: 18.2 d B-1 DT_{50}: 89.7 d (SFO) DT_{90}: 298 d		
	^{14}C-A-ring Cyflumetofen	**Netherlands systems** **Goorven system** pH 4.56-5.13, 0.81% OC	DT_{50}: 10.8 d (SFO) DT_{90}: 35.9 d	Non-persistent	2146936
		Schoonrewoerdsewiel system pH 7.17-7.23, 6.2% OC	DT_{50}: 0.19 d (IORE) DT_{90}: 1.3 d Representative t½: 0.39 d		

Study	Test substance	Study conditions	Results / Values	Comments	PMRA Reference
	^{14}C-B-ring Cyflumetofen	**Netherlands systems** **Goorven system** pH 4.56-5.54, 0.81% OC **Schoonrewoerdsewiel system** pH 7.17-7.36, 6.2% OC	DT_{50}: 14.6 d (SFO) DT_{90}: 48.5 d Cyflumetofen DT_{50}: 0.08 d (IORE) DT_{90}: 0.65 d Representative t½: 0.20 d B-1 DT_{50}: 320 d (SFO) DT_{90}: 1065 d	Cyflumetofen: Non-persistent B-1: Persistent	2146939
Anaerobic bio-transformation in water/ sediment system	Cyflumetofen ^{14}C-A-ring and ^{14}C-B-ring	**Florida system** pH 6.2 (sed.)/7.3 (water), 3.83% OC (combined labels) **Pennsylvania system** pH 5.0 (sed.)/6.0 (water), 1.86% OC (combined labels)	DT_{50}: 17.5 d (IORE) DT_{90}: 70.7 d Representative t½ : 21.3 d DT_{50}: 4.11 d (IORE) DT_{90}: 15.7 d Representative t½ : 4.73 d	Non-persistent to slightly persistent	2146934
Bio-accumulation in fish	^{14}C-B-ring Cyflumetofen	Common carp 21-day exposure period 32-day depuration period	**Bioconcentration factors <250** Based on total radioactive material, not specifically based on radio-labelled parent.	Cyflumetofen and its transformation products are not expected to bioaccumulate in fish	2146987
Terrestrial field dissipation					
Terrestrial field dissipation	Cyflumetofen	**New York silt loam soil**[1] (Ecoregion 8.1)	Cyflumetofen DT_{50}: 10.8 d (SFO) DT_{90}: 35.8 d B-1 DT_{50}: 12.9 d (SFO) DT_{90}: 43.0 d	Cyflumetofen: Non-persistent B-1: Non-persistent	2146909
Freezer storage stability	Cyflumetofen and transformation products	Cyflumetofen was unstable under freezer storage at -10°C after 60 days, while the transformation products tested (A-2, B-1, B-3, and AB-1 dimer) are more stable under freezer storage at -10°C over two years.		Care should be taken while interpreting the results from this field dissipation study	2146856

[1] The freezer storage stability study (interim, one-year storage only) found that cyflumetofen was not stable after 60 days in conditions ≤-10°C in the California, Washington and Florida soils. The samples for all field locations were stored for an average of 2 years, therefore, the results obtained for California, Washington and Florida are not acceptable. See the details of the Freezer Storage Stability study results.

Table 13 Screening Level Estimated Environmental Concentrations for Cyflumetofen and Several Transformation Products in Soil, on Foliage, and in Water

Compound	Molecular weight ratio to Cyflumetofen	EEC in Soil (mg a.i./kg soil)	EEC on Soil (g a.i./ha)	EEC on Foliage (g a.i./ha)	Aquatic EEC (µg a.i./L)	
					Permanent water bodies (80 cm)	Non-permanent / Shallow water bodies (15 cm)
Cyflumetofen	N/R	0.099	223.8	275.8	39.7	212
B-1	190.1/447.5 = 0.425	0.142	N/R	N/R	16.9[1]	90.1[1]
B-2	362.2/447.5 = 0.809	N/R	N/R	N/R	32.1[1]	N/R
A-2	207.2/447.5 = 0.752	N/R	N/R	N/R	15.4[1]	82.1[1]
AB-1	345.4/447.5 = 0.772	0.141	N/R	N/R	30.6[1]	N/R
AB-11	431.5/447.5 = 0.964	N/R	N/R	N/R	38.3[1]	N/R

[1] The EEC for each transformation product tested was calculated using the parent:transformation product molecular weight (MW) ratio, assuming 100% conversion of the parent to the transformation product.

Table 14 Screening level Estimated Environmental Concentrations for Cyflumetofen in Vegetation and Insects After Two Direct Applications of 200 g a.i./ha (14-day interval between applications)

Environmental Compartment	Maximum residue concentrations			Mean residue concentrations		
	Concentration fresh weight (mg a.i./kg)	Fresh/Dry weight ratios	Concentration dry weight (mg a.i./kg)	Concentration fresh weight (mg a.i./kg)	Fresh/Dry weight ratios	Concentration dry weight (mg a.i./kg)
short range grass	59.0227	3.3	**194.78**	20.9614	3.3	**69.17**
long grass	27.0285	4.4	**118.93**	8.8256	4.4	**38.83**
forage crops	33.3720	5.4	**180.21**	11.0321	5.4	**59.57**
small insects	14.3417	3.8	**54.50**	7.9982	3.8	**30.39**
pods with seeds	3.5854	3.9	**13.98**	1.7100	3.9	**6.67**
large insects	3.5854	3.8	**13.62**	1.7100	3.8	**6.50**
grain and seeds	3.5854	3.8	**13.62**	1.7100	3.8	**6.50**
fruit	3.5854	7.6	**27.25**	1.7100	7.6	**13.00**

Table 15 Refined Tier 1 Aquatic Estimated Environmental Concentrations for Cyflumetofen Based on Spray Drift Input Only

Test Substance	Water body depth scenario	Initial EEC (no refinement)	EEC Field Sprayer (6% drift)	EEC Early Season Airblast (74% drift)	EEC Late Season Airblast (59% drift)
Cyflumetofen	80 cm	39.7 µg a.i./L	2.38 µg a.i./L	29.4 µg a.i./L	23.4 µg a.i./L
Cyflumetofen	15 cm for amphibians	212 µg a.i./L	12.7 µg a.i./L	157µg a.i./L	125 µg a.i./L
B-2 (molecular weight: 362.2)	80 cm	32.1 µg B-2/L	1.93 µg B-2/L	23.8 µg B-2/L	18.9 µg B-2/L

Table 16 Level 1 Aquatic Ecoscenario Modelling Estimated Environmental Concentrations for Cyflumetofen in a Water Body 0.15 m Deep, Excluding Spray Drift, Overlying Water

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use 2 × 0.2 kg a.i./ha, at 14-day intervals						
BC	0.002	<0.001	<0.001	<0.001	<0.001	<0.001
ON	0.059	0.008	0.002	<0.001	<0.001	<0.001
QC	0.058	0.007	0.002	<0.001	<0.001	<0.001
Atlantic	0.15	0.019	0.004	0.002	0.001	<0.001
Grape use 2 × 0.2 kg a.i./ha, at 14-day intervals						
ON	0.50	0.069	0.018	0.007	0.005	0.001
Tomato use 2 × 0.2 kg a.i./ha, at 14-day intervals						
ON	0.85	0.11	0.032	0.013	0.009	0.002
Strawberry use 2 × 0.2 kg a.i./ha, at 14-day intervals						
BC	0.045	0.006	0.001	<0.001	<0.001	<0.001

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Prairie	3.7	0.48	0.098	0.039	0.027	0.007
Atlantic	4.0	0.75	0.22	0.085	0.058	0.015

Table 17 **Level 1 Aquatic Ecoscenario Modelling Estimated Environmental Concentrations for Cyflumetofen in a Water body 0.80 m Deep, Excluding Spray Drift, Overlying Water**

Region	EEC (µg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apple use 2 × 0.2 kg a.i./ha, at a 14-day interval						
BC	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ON	0.011	0.002	<0.001	<0.001	<0.001	<0.001
QC	0.011	0.001	<0.001	<0.001	<0.001	<0.001
Atlantic	0.028	0.004	<0.001	<0.001	<0.001	<0.001
Grape use 2 × 0.2 kg a.i./ha, at a 14-day interval						
ON	0.093	0.013	0.004	0.002	0.001	<0.001
Tomato use 2 × 0.2 kg a.i./ha, at a 14-day interval						
ON	0.16	0.022	0.007	0.003	0.002	<0.001
Strawberry use 2 × 0.2 kg a.i./ha, at a 14-day interval						
BC	0.008	0.001	<0.001	<0.001	<0.001	<0.001
Prairie	0.69	0.095	0.022	0.010	0.007	0.002
Atlantic	0.76	0.14	0.048	0.022	0.015	0.004

Table 18 **Toxicity of Cyflumetofen and Some Major Transformation Products to Non-Target Terrestrial Species**

Organism	Exposure	Test substance	Result	PMRA Reference
Earthworm *(Eisenia fetida)*	14-day acute	Cyflumetofen	LC_{50} >1000 mg a.i./kg soil dw	2147026
		Cyflumetofen 20% SC	LC_{50} >1050 mg a.i./kg soil dw	2145835
		B-1	LC_{50} >1000 mg a.i./kg soil dw	2147024
		AB-1	LC_{50} >1000 mg a.i./kg soil dw	2147022
	56-day chronic	Cyflumetofen	NOEC: 1000 mg a.i./kg soil dw (no effects at highest test concentration)	2147028
Honey bee (*Apis mellifera*)	96-hr oral	*Cyflumetofen 20% SC*	LD_{50} >116 µg a.i./bee	2145811
	96-hr contact	Cyflumetofen	LD_{50} >100 µg a.i./bee	2147020
	48-hr contact	*Cyflumetofen 20% SC*	LD_{50} >100 µg a.i./bee	2145814
Parasitic wasp (*Aphidius rhopalosiphi*)	48-hr acute (glass plate)	*Cyflumetofen 20% SC*	LR_{50}>1.4kg a.i./ha	2145817
Predatory mite (*Typhlodromus pyri*)	7-day acute (glass plate)	*Cyflumetofen 20% SC*	LR_{50}>1.4kg a.i./ha	2145819
Northern bobwhite quail (*Colinus virginianus*)	14-day acute oral	Cyflumetofen	LD_{50} >2000 mg a.i./kg bw/day	2146946
	5-day dietary	Cyflumetofen	LC_{50} >5003 mg a.i./kg diet, equivalen to >1340 mg a.i./kg-bw/day	2146950

Organism	Exposure	Test substance	Result	PMRA Reference
	Reproduction	Cyflumetofen	NOEC: 154 mg a.i./kg diet, equivalent to 13.6 mg a.i./kg-bw/day (increased eggs cracked per pen)	2146951
Mallard duck (*Anas platyrhynchos*)	14-day acute oral	Cyflumetofen	LD_{50} >2250 mg a.i./kg bw/day	2146941
	5-day dietary	Cyflumetofen	LC_{50} >5760 mg a.i./kg diet, equivalent to >3784 mg a.i./kg-bw/day	2146948
	Reproduction	Cyflumetofen	NOEC: 930 mg a.i./kg diet, equivalent to 114.6 mg a.i./kg-bw/day (no effect at highest dose tested)	2146959
Zebra finch (*Taeniopygia guttata*)	14-day acute oral	Cyflumetofen	LD_{50} >2000 mg a.i./kg bw/day	2146943
Wistar Rat	15-day acute oral	Cyflumetofen	LD_{50} >2000 mg/kg bw	2146782
	Reproduction (multi-generation)	Cyflumetofen	NOAEL: 46.6 mg/kg bw/day (♀) (reduced estradiol, FSH, progesterone, increased estrous cycle length)	2146828
Monocots: Corn (*Zea mays*), oat (*Avena sativa*), onion (*Allium cepa*), ryegrass (*Lolium perenne*) **Dicots:** Sugar beet (*Beta vulgaris*), cucumber (*Cucumis sativus*), lettuce (*Lactuca sativa*), tomato (*Lycopersicon esculentum*), radish (*Raphanus sativus*), soybean (*Glycine max*)	21-day seedling emergence, Tier II test (dose-response)	*Cyflumetofen 20% SC*	No EC_{25} values could be determined for monocots Most sensitive dicot: **Tomato** EC_{25}: 44.0 g a.i./ha (dry weight)	2145842
	21-day vegetative vigour, Tier II test (dose-response)	*Cyflumetofen 20% SC*	EC_{25} : >306 g a.i./ha (sugarbeet, cucumber, lettuce, tomato, radish) >300 g a.i./ha (oat, ryegrass, soybean) >280 g a.i./ha (corn, onion)	2145838

Table 19 Screening Level Risk Assessment on Non-target Terrestrial Organisms Other than Birds and Mammals

Organism	Exposure [PMRA reference]	Test substance	Endpoint value	EEC	RQ	LOC exceeded?
Earthworm *(Eisenia fetida)*	Acute [2147026]	Cyflumetofen	0.5 × 14-d LC_{50} >500 mg a.i./kg soil dw	0.099 mg a.i./kg soil dw	<0.0002	No
	Acute [2145835]	*Cyflumetofen 20% SC*	0.5 × 14-d LC_{50} >525 mg a.i./kg soil dw	0.099 mg a.i./kg soil dw	<0.0002	No
	Acute [2147024]	B-1	0.5 × 14-d LC_{50} >500 mg a.i./kg soil dw	0.142 mg B-1/kg soil dw	<0.0003	No

Organism	Exposure [PMRA reference]	Test substance	Endpoint value	EEC	RQ	LOC exceeded?
	Acute [2147022]	AB-1	0.5 × 14-d LC_{50} >500 mg a.i./kg soil dw	0.141 mg AB-1/kg soil dw	<0.0003	No
	Chronic [2147028]	Cyflumetofen	28-d and 58-d NOEC: 1000 mg a.i./kg soil dw (no effects at highest test concentration)	0.099 mg a.i./kg soil dw	<0.0001	No
Honey bee (*Apis mellifera*)	Acute [2145811]	*Cyflumetofen 20% SC*	96-hr LD_{50} >116 µg a.i./bee	5.8 µg a.i./bee	<0.05	No
	Acute [2147020]	Cyflumetofen	96-hr LD_{50} >100 µg a.i./bee	0.48 µg a.i./bee	<0.005	No
	Acute [2145814]	*Cyflumetofen 20% SC*	48-hr LD_{50} >100 µg a.i./bee	0.48 µg a.i./bee	<0.005	No
Parasitic wasp (*Aphidius rhopalosiphi*)	Acute [2145817]	*Cyflumetofen 20% SC*	48-hr LR_{50} >1.4 kg a.i./ha	275.80 g a.i./ha	<0.197	No
Predatory mite (*Typhlodromus pyri*)	Acute [2145819]	*Cyflumetofen 20% SC*	7-d LR_{50} >1.4 kg a.i./ha	275.80 g a.i./ha	<0.197	No
Monocots: corn (*Zea mays*), oat (*Avena sativa*), onion (*Allium cepa*), ryegrass (*Lolium perenne*) **Dicots:** sugar beet (*Beta vulgaris*), cucumber (*Cucumis sativus*), lettuce (*Lactuca sativa*), tomato (*Lycopersicon esculentum*), radish (*Raphanus sativus*), soybean (*Glycine max*)	Seedling emergence [2145842]	*Cyflumetofen 20% SC*	Most sensitive dicot: **Tomato** 21-d EC_{25}: 44.0 g a.i./ha	***In-field exposure*** 223.8 g a.i./ha	**5.09**	**Yes**
	Vegetative vigour [2145838]	*Cyflumetofen 20% SC*	21-d EC_{25} >: >306 g a.i./ha (sugarbeet, cucumber, lettuce, tomato, radish) >300 g a.i./ha (oat, ryegrass, soybean) >280 g a.i./ha (corn, onion)	***In-field exposure*** 275.8 g a.i./ha	<0.901 <0.912 <0.985	No No No

Table 20 Screening Level Risk Assessment for Birds and Mammals, On-field Exposure, Based on Maximum Residues Unless Otherwise Specified

Study type	Toxicity (mg a.i./kg bw/d)	Feeding Guild (food item)	EDE[a] (mg a.i./kg bw)	Risk Quotient	LOC exceeded?
Small Bird (0.02 kg)					
Acute	200.0	Insectivore (small insects)	13.90	<0.07	No
Reproduction	13.6	Insectivore (small insects)	13.90 (maximum residues)	**1.02**	**Yes**
			7.75 (mean residues)	0.57	No
Medium Sized Bird (0.1 kg)					
Acute	200.00	Insectivore (small insects)	10.85	<0.05	No
Reproduction	13.6	Insectivore (small insects)	10.85	0.80	No
Large Sized Bird (1 kg)					
Acute	200.0	Herbivore (short grass)	11.32	<0.06	No
Reproduction	13.6	Herbivore (short grass)	11.32	0.83	No
Small Mammal (0.015 kg)					
Acute	200.0	Insectivore (small insects)	7.99	<0.04	No
Reproduction	46.6	Insectivore (small insects)	7.99	0.17	No
Medium Sized Mammal (0.035 kg)					
Acute	200.0	Herbivore (short grass)	25.04	<0.13	No
Reproduction	46.6	Herbivore (short grass)	25.04	0.54	No
Large Sized Mammal (1 kg)					
Acute	200.0	Herbivore (short grass)	13.38	<0.07	No
Reproduction	46.6	Herbivore (short grass)	13.38	0.29	No

[a] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/bw) × EEC, where:

FIR: Food Ingestion Rate. For generic birds with body weight less than or equal to 200 g, the "passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:

Passerine Equation (body weight <or =200 g): FIR (g dry weight/day) = $0.398(\text{bw in g})^{0.850}$

All birds Equation (body weight >200 g): FIR (g dry weight/day) = $0.648(\text{bw in g})^{0.651}$

For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = $0.235(\text{bw in g})^{0.822}$

bw: Generic Body Weight

EEC: Concentration of pesticide on food item. At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 21 Refined Risk Assessment on Non-target Terrestrial Plants (Off-field Spray Drift Exposure)

Organism	Exposure [PMRA reference]	Test substance	Endpoint value	EEC	RQ	LOC exceeded?
Dicots: Sugarbeet cucumber lettuce tomato radish soybean	Seedling emergence [2145842]	***Cyflumetofen 20% SC***	Most sensitive dicot: **Tomato** 21-d EC_{25}: 44.0 g a.i./ha	***Off-field exposure***[a] ***74% drift***[1]: 165.6 g a.i./ha ***59% drift***[2]: 132.0 g a.i./ha ***6% drift***[3]: 13.4 g a.i./ha	74% drift: **3.76** 59% drift: **3.00** 6% drift: 0.30	**Yes** **Yes** No

a. Amount of drift deposition estimated at 1 m downwind of the edge of the site of application, represented as a percentage of the full application rate:

1. Early season airblast
2. Late season airblast
3. Field sprayer

Table 22 Toxicity of Cyflumetofen and Some Major Transformation Products to Aquatic Organisms

Test species	Exposure	Test substance	Result	PMRA Reference
Rainbow trout (*Oncorhynchus mykiss*)	96-hr acute	Cyflumetofen	LC$_{50}$ >17.5 µg a.i./L	2146979
		B-1	LC$_{50}$ >97.9 mg a.i./L	2146982
		A-2	LC$_{50}$: 7.09 mg a.i./L	2146981
		Cyflumetofen 20% SC	LC$_{50}$ >837 µg a.i./L	2145804
Fathead minnow (*Pimephales promelas*)	96-hr acute	Cyflumetofen	LC$_{50}$ >29.2 µg a.i./L	2146980
	34-day chronic, Early-life stage	Cyflumetofen	NOEC: 31.6 µg a.i./L (no effects at highest test concentration)	2146984
Common carp (*Cyprinus carpio*)	28-day chronic, Juvenile fish	Cyflumetofen (solvent used)	NOEC: 72 µg a.i./L (growth rate)	2146986
Daphnia magna	48-hr acute	Cyflumetofen	EC$_{50}$ >17.2 µg a.i./L	2146989
		B-1	EC$_{50}$ >177.5 mg a.i./L	2146990
		B-2	EC$_{50}$ >0.020 mg a.i./L	2146991
		A-2	EC$_{50}$: 10.52 mg a.i./L	2146993
		Cyflumetofen 20% SC	EC$_{50}$ >744 µg a.i./L	2145807
	21-day chronic, reproduction	Cyflumetofen	NOEC: 16.2 µg a.i./L (no effects at highest test concentration)	2146995
Green algae (*Pseudo-kirchneriella subcapitata*)	96-hr acute	Cyflumetofen	EC$_{50}$ >23.8 µg a.i./L	2147005
	72-hr acute	*Cyflumetofen 20% SC*	EC$_{50}$ >340 µg a.i./L	2145809
	96-hr acute	B-1	EC$_{50}$ >102.7 mg a.i./L	2146997
	72-hr acute	AB-11	EC$_{50}$ >0.483 mg a.i./L	2147006
Blue-green algae (*Anabaena flos-aquae*)	96-hr acute	Cyflumetofen	EC$_{50}$ >31.5 µg a.i./L	2147003
Diatom (*Navicula pelliculosa*)	96-hr acute	Cyflumetofen	EC$_{50}$ >34.3 µg a.i./L	2146999
Duckweed (*Lemna gibba*)	7-day acute	Cyflumetofen	EC$_{50}$ >38.3 µg a.i./L	2147017
Midge (*Chironomus riparius*)	28-day chronic *Spiked water*	Cyflumetofen	NOEC: 65.9 µg a.i./L (no effects at highest test concentration)	2147010
	28-day chronic *Spiked sediments*[a]	Cyflumetofen	NOEC: 26.5 mg a.i./kg dw [sediments] 0.12 µg a.i./L [pore water] 0.03 µg a.i./L [overlying water] (emergence rate)	2147014
		AB-1	NOEC: 36.1 mg a.i./kg dw [sediments] 34.2 mg a.i./L [pore water] 9.06 mg a.i./L [overlying water] (emergence rate)	2147012
		AB-1dimer	NOEC: 75.3 mg a.i./kg dw [sediments] 5.61µg a.i./L [pore water] 27.4 µg a.i./L [overlying water] (no effects at highest test concentration)	2147015
Sheepshead minnow (*Cyprinodon variegatus*)	96-hr acute	Cyflumetofen	LC$_{50}$ >7.59 µg a.i./L	2146965

Test species	Exposure	Test substance	Result	PMRA Reference
Saltwater diatom (*Skeletonema costatum*)	96-hr acute	Cyflumetofen	EC$_{50}$ >33.6 µg a.i./L	2147001
Eastern oyster (*Crassostrea virginica*)	96-hr acute	Cyflumetofen	EC$_{50}$ >6.30 µg a.i./L	2146967
Mysid shrimp (*Americamysis bahia*)	96-hr acute	Cyflumetofen	LC$_{50}$ >22.7 µg a.i./L	2146969
Amphipod (*Leptocheirus plumulosus*)	10-day acute *Spiked sediments*[a]	Cyflumetofen (solvent used)	LC$_{50}$: >787 mg a.i./kg dw [sediments] >19.7 mg a.i./L [pore water] >5.17 mg a.i./L [overlying water]	2147008

a Generally, spiked water tests are preferred because the application of the TGAI to the water column is a more realistic exposure scenario when considering potential entry into the aquatic environment. Thus, no screening-level risk assessment or Tier 1 risk assessment are performed for the chronic exposure of freshwater chironomids to cyflumetofen and major transformation products AB-1 and AB-1 dimer from spiked sediments.

Table 23 Screening Level Risk Assessment for Aquatic Organisms

Organism	Exposure [PMRA Reference]	Test substance	Endpoint value	EEC (µg a.i./L)	RQ	LOC exceeded?
Rainbow trout (*Oncorhynchus mykiss*)	Acute [2146979]	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >1.75 µg a.i./L	39.7	**<22.7**	**Unlikely**[a]
	Acute [2145804]	*Cyflumetofen 20% SC*	0.1 × 96-hr LC$_{50}$ >83.7 µg a.i./L	39.7	<0.47	No
	Acute [2146982]	B-1	0.1 × 96-hr LC$_{50}$ >9.79 mg a.i./L	16.9	<0.002	No
	Acute [2146981]	A-2	0.1 × 96-hr LC$_{50}$: 0.709 mg a.i./L	15.4	0.022	No
Fathead minnow (*Pimephales promelas*)	Acute [2146980]	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >2.92 µg a.i./L	39.7	**<13.6**	**Unlikely**[a]
	Chronic *Early-life stage* [2146984]	Cyflumetofen	34-d NOEC: 31.6 µg a.i./L (no effects at highest test concentration)	39.7	**1.26**	**Unlikely** (Based on an endpoint where no effects were observed)
Common carp (*Cyprinus carpio*)	Chronic *juvenile fish* [2146986]	Cyflumetofen	28-d NOEC: 72 µg a.i./L (growth rate)	39.7	0.55	No
Amphibians	Acute [2146979]	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >1.75 µg a.i./L [Rainbow trout]	212	**<121**	**Unlikely**[a]
	Acute [2145804]	*Cyflumetofen 20% SC*	0.1 × 96-hr LC$_{50}$ >83.7 µg a.i./L [Rainbow trout]	212	**<2.53**	**Unlikely**[a]
	Chronic juvenile fish [2146986]	Cyflumetofen	28-d NOEC: 72 µg a.i./L (growth rate) [Common carp]	212	**2.94**	**Yes**
	Acute [2146982]	B-1	0.1 × 96-hr LC$_{50}$ >9.79 mg a.i./L [Rainbow trout]	90.1	<0.009	No

Organism	Exposure [PMRA Reference]	Test substance	Endpoint value	EEC (µg a.i./L)	RQ	LOC exceeded?
	Acute [2146981]	A-2	0.1 × 96-hr LC_{50}: 0.709 mg a.i./L [Rainbow trout]	82.1	0.12	No
Daphnia magna	Acute [2146989]	Cyflumetofen	0.5 × 48-hr EC_{50} >8.6 µg a.i./L	39.7	**<4.62**	**Unlikely**[a]
	Acute [2146990]	B-1	0.5 × 48-hr EC_{50} >88.75 mg a.i./L	16.9	<0.0002	No
	Acute [2146991]	B-2	0.5 × 48-hr EC_{50} >0.010 mg a.i./L	32.1	**<3.21**	**Unlikely**[a]
	Acute [2146993]	A-2	0.5 × 48-hr EC_{50}: 5.26 mg a.i./L	15.4	0.003	No
	Acute [2145807]	*Cyflumetofen 20% SC*	0.5 × 48-hr EC_{50} >372 µg a.i./L	39.7	<0.11	No
	Chronic [2146995]	Cyflumetofen	21-d NOEC: 16.2 µg a.i./L (no effects at highest test concentration)	39.7	**2.45**	**Unlikely** (Based on an endpoint where no effects were observed)
Green algae (*Pseudo-kirchneriella subcapitata*)	Acute [2147005]	Cyflumetofen	0.5 × 96-hr EC_{50} >11.9 µg a.i./L	39.7	**<3.34**	**Unlikely**[a]
	Acute [2145808]	*Cyflumetofen 20% SC*	0.5 × 72-hr EC_{50} >170 µg a.i./L	39.7	<0.23	No
	Acute [2146997]	B-1	0.5 × 96-hr EC_{50} >51.35 mg a.i./L	16.9	<0.0003	No
	Acute [2147006]	AB-11	0.5 × 72-hr EC_{50} >0.242 mg a.i./L	38.3	<0.16	No
Blue-green algae (*Anabaena flos-aquae*)	Acute [2147003]	Cyflumetofen	0.5 × 96-hr EC_{50} >15.75 µg a.i./L	39.7	**<2.52**	**Unlikely**[a]
Diatom (*Navicula pelliculosa*)	Acute [2146999]	Cyflumetofen	0.5 × 96-hr EC_{50} >17.15 µg a.i./L	39.7	**<2.31**	**Unlikely**[a]
Duckweed (*Lemna gibba*)	Acute [2147017]	Cyflumetofen	0.5 × 7-d EC_{50} >19.15 µg a.i./L	39.7	**<2.07**	**Unlikely**[a]
Midge (*Chironomus riparius*)	Chronic *Spiked water* [2147010]	Cyflumetofen	28-d NOEC: 65.9 µg a.i./L (no effects at highest test concentration)	39.7	0.60	No
Sheepshead minnow (*Cyprinodon variegatus*)	Acute [2146965]	Cyflumetofen	0.1 × 96-hr LC_{50} >0.759 µg a.i./L	39.7	**<52.3**	**Unlikely**[a]
Saltwater diatom (*Skeletonema costatum*)	Acute [2147001]	Cyflumetofen	0.5 × 96-hr EC_{50} >16.8 µg a.i./L	39.7	**<2.36**	**Unlikely**[a]
Eastern oyster (*Crassostrea virginica*)	Acute [2146967]	Cyflumetofen	0.5 × 96-hr EC_{50} >3.15 µg a.i./L	39.7	**<12.6**	**Unlikely**[a]
Mysid shrimp (*Americamysis bahia*)	Acute [2146969]	Cyflumetofen	0.5 × 96-hr LC_{50} >11.35 µg a.i./L	39.7	**<3.50**	**Unlikely**[a]

[a] The RQs are reported as lesser than values as no definitive toxicological effects were observed at any of the tested concentrations. However, the acute risk quotient for the organisms exposed to the formulated product *Cyflumetofen 20% SC* did not exceed the LOC. The SC formulation effectively increased the solubility of the TGAI in the test solutions. Although a definitive toxicity value was not attained with *Cyflumetofen 20% SC*, these results indicated that cyflumetofen alone is

unlikely to pose a risk to freshwater organisms at these levels.

Table 24 Refined Risk Assessment for Aquatic Organisms Based on Spray Drift Inputs

Organism	Exposure	Test Substance	Endpoint Value	Field Sprayer (6% drift)		Early Season Airblast (74%drift)		Late Season Airblast (59% drift)		LOC exceeded?
				EEC (µg/L)	RQ	EEC (µg/L)	RQ	EEC (µg/L)	RQ	
Rainbow trout	Acute	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >1.75 µg a.i./L	2.38	**<1.36**	29.4	**<16.8**	23.4	**<13.4**	**Unlikely**[a]
	Acute	*Cyflumetofen 20% SC*	0.1 × 96-hr LC$_{50}$: >83.7 µg a.i./L	2.38	<0.028	29.4	<0.35	23.4	<0.28	No (Results presented here for comparison purposes with the TGAI endpoint)
Fathead minnow	Acute	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >2.92 µg a.i./L	2.38	<0.82	29.4	**<10.1**	23.4	**<8.01**	**Unlikely**[a]
	Chronic ELS	Cyflumetofen	34-d NOEC: 31.6 µg a.i./L	2.38	0.08	29.4	0.93	23.4	0.74	No
Amphibians [assessment for amphibians is based on data for most sensitive fish species]	Acute	Cyflumetofen	0.1 × 96-hr LC$_{50}$ >1.75 µg a.i./L [Rainbow trout]	12.7	**<7.26**	157	**<89.7**	125	**<71.4**	**Unlikely**[a]
	Acute	*Cyflumetofen 20% SC*	0.1 × 96-hr LC$_{50}$: >83.7 µg a.i./L [Rainbow trout]	12.7	<0.15	157	**<1.88**	125	**<1.49**	**Unlikely**[a]
	Chronic	Cyflumetofen	28-d NOEC: 72 µg a.i./L (growth rate) [Common carp]	12.7	0.17	157	**2.18**	125	**1.74**	**Yes**
D. magna	Acute	Cyflumetofen	0.5 × 48-hr EC$_{50}$ >8.6 µg a.i./L	2.38	<0.28	29.4	**<3.42**	23.4	**<2.72**	**Unlikely**[a]
	Acute	*Cyflumetofen 20% SC*	0.5 × 48-hr EC$_{50}$: >372 µg a.i./L	2.38	<0.006	29.4	<0.08	23.4	<0.06	No (Results presented here for comparison purposes with the TGAI endpoint)
	Chronic	Cyflumetofen	21-d NOEC: 16.2 µg a.i./L	2.38	0.15	29.4	**1.82**	23.4	**1.44**	**Unlikely** (Based on an endpoint where no effects were observed)
	Acute	B-2	0.5 × 48-hr EC$_{50}$ >0.010 mg a.i./L	1.93	<0.19	23.8	**<2.38**	18.9	**<1.89**	**Unlikely**[a]
P. subcapitata	Acute	Cyflumetofen	0.5 × 96-hr EC$_{50}$ >11.9 µg a.i./L	2.38	<0.20	29.4	**<2.47**	23.4	**<1.97**	**Unlikely**[a]
	Acute	*Cyflumetofen 20% SC*	0.5 × 72-hr EC$_{50}$:>170 µg a.i./L	2.38	<0.014	29.4	<0.17	23.4	<0.14	No (Results presented here for comparison purposes with the TGAI

Organism	Exposure	Test Substance	Endpoint Value	Field Sprayer (6% drift)		Early Season Airblast (74%drift)		Late Season Airblast (59% drift)		LOC exceeded?
				EEC (µg/L)	RQ	EEC (µg/L)	RQ	EEC (µg/L)	RQ	
										endpoint)
A. flos-aquae	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >15.75 µg a.i./L	2.38	<0.15	29.4	**<1.87**	23.4	**<1.49**	**Unlikely**[a]
N. pelliculosa	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >17.15 µg a.i./L	2.38	<0.14	29.4	**<1.71**	23.4	**<1.36**	**Unlikely**[a]
Duckweed	Acute	Cyflumetofen	0.5 × 7-d EC_{50} >19.15 µg a.i./L	2.38	<0.12	29.4	**<1.54**	23.4	**<1.22**	**Unlikely**[a]
Sheepshead minnow	Acute	Cyflumetofen	0.1 × 96-hr LC_{50} >0.759 µg a.i./L	2.38	**<3.14**	29.4	**<38.7**	23.4	**<30.1**	**Unlikely**[a]
S. costatum	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >16.8 µg a.i./L	2.38	<0.14	29.4	**<1.75**	23.4	**<1.39**	**Unlikely**[a]
Eastern oyster	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >3.15 µg a.i./L	2.38	<0.76	29.4	**<9.33**	23.4	**<7.43**	**Unlikely**[a]
Mysid shrimp	Acute	Cyflumetofen	0.5 × 96-hr LC_{50} >11.35 µg a.i./L	2.38	<0.21	29.4	**<2.59**	23.4	**<2.06**	**Unlikely**[a]

[a] The RQs are reported as lesser than values as no definitive toxicological effects were observed at any of the tested concentrations. However, the acute risk quotient for the organisms exposed to the formulated product *Cyflumetofen 20% SC* did not exceed the LOC. Although a definitive toxicity value was not attained with *Cyflumetofen 20% SC*, these results indicated that cyflumetofen alone is unlikely to pose a risk to freshwater organisms at these levels.

Table 25 Refined Risk Assessment for Aquatic Organisms Based on Runoff Inputs

Organism	Exposure	Test Substance	Endpoint Value	Most Conservative Use Scenario: Atlantic strawberries		LOC exceeded?
				EEC [µg/L] (sampling time)	RQ	
Rainbow trout	Acute	Cyflumetofen	0.1 × 96-hr LC_{50} >1.75 µg a.i./L	0.14 (96-hr)	<0.08	No
	Acute	*Cyflumetofen 20% SC*	0.1 × 96-hr LC_{50}: >83.7 µg a.i./L	0.14 (96-hr)	<0.002	No (Results presented here for comparison purposes with the TGAI endpoint)
Fathead minnow	Acute	Cyflumetofen	0.1 × 96-hr LC_{50} >2.92 µg a.i./L	0.14 (96-hr)	<0.05	No
	Chronic ELS	Cyflumetofen	34-d NOEC: 31.6 µg a.i./L	0.048 (21-d)	0.002	No
Amphibians [assessment for amphibians is based on data for most sensitive fish species]	Acute	Cyflumetofen	0.1 × 96-hr LC_{50} >1.75 µg a.i./L [Rainbow trout]	0.75 (96-hr)	<0.43	No
	Acute	*Cyflumetofen 20% SC*	0.1 × 96-hr LC_{50}: >83.7 µg a.i./L [Rainbow trout]	0.75 (96-hr)	<0.009	No
	Chronic	Cyflumetofen	28-d NOEC: 72 µg a.i./L (growth rate) [Common carp]	0.22 (21-d)	0.003	No

Organism	Exposure	Test Substance	Endpoint Value	Most Conservative Use Scenario: Atlantic strawberries		LOC exceeded?
				EEC [µg/L] (sampling time)	RQ	
D. magna	Acute	Cyflumetofen	0.5 × 48-hr EC_{50} >8.6 µg a.i./L	0.76 (peak)	<0.09	No
	Acute	*Cyflumetofen 20% SC*	0.5 × 48-hr EC_{50}: >372 µg a.i./L	0.76 (peak)	<0.002	No (Results presented here for comparison purposes with the TGAI endpoint)
	Chronic	Cyflumetofen	21-d NOEC: 16.2 µg a.i./L	0.048 (21-d)	0.003	No
	Acute	B-2	0.5 × 48-hr EC_{50} >0.010 mg a.i./L	0.62 (peak) [using molecular weight ratio]	<0.06	No
P. subcapitata	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >11.9 µg a.i./L	0.14 (96-hr)	<0.01	No
	Acute	*Cyflumetofen 20% SC*	0.5 × 72-hr EC_{50} >170 µg a.i./L	0.14 (96-hr)	<0.0008	No (Results presented here for comparison purposes with the TGAI endpoint)
A. flos-aquae	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >15.75 µg a.i./L	0.14 (96-hr)	<0.009	No
N. pelliculosa	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >17.15 µg a.i./L	0.14 (96-hr)	<0.008	No
Duckweed	Acute	Cyflumetofen	0.5 × 7-d EC_{50} >19.15 µg a.i./L	0.14 (96-hr)	<0.007	No
Sheepshead minnow	Acute	Cyflumetofen	0.1 × 96-hr LC_{50} >0.759 µg a.i./L	0.14 (96-hr)	<0.18	No
S. costatum	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >16.8 µg a.i./L	0.14 (96-hr)	<0.008	No
Eastern oyster	Acute	Cyflumetofen	0.5 × 96-hr EC_{50} >3.15 µg a.i./L	0.14 (96-hr)	<0.04	No
Mysid shrimp	Acute	Cyflumetofen	0.5 × 96-hr LC_{50} >11.35 µg a.i./L	0.14 (96-hr)	<0.01	No

Table 26 Alternative Active Ingredients Registered for Uses of Nealta Miticide

Mode-of-Action Group	Active Ingredient	Crops	Pest Species
1A	Formetanate hydrochloride	Apple Pear	European red mite Twospotted spider mite
6	Abamectin	Apple Pear	European red mite Twospotted spider mite McDaniel spider mite
		Grape	European red mite Twospotted spider mite
		Strawberry	Twospotted spider mite

Mode-of-Action Group	Active Ingredient	Crops	Pest Species
			McDaniel spider mite
10A	Clofentezine	Apple Pear	European red mite Twospotted spider mite McDaniel spider mite
		Strawberry	Twospotted spider mite
20B	Acequinocyl	Apple Pear	European red mite Twospotted spider mite
21A	Pyridaben	Apple Pear Grape Strawberry	European red mite Twospotted spider mite McDaniel spider mite
23	Spirodiclofen	Pome fruits Grape	European red mite Twospotted spider mite McDaniel spider mite
UN	Bifenazate	Apple	European red mite Twospotted spider mite McDaniel spider mite
		Grape	European red mite Twospotted spider mite
N/A	Mineral oil	Apple Pear	European red mite (overwintering eggs)

Table 27 Toxic Substances Management Policy Considerations - Comparison of Cyflumetofen and Its Major Transformation Products to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes.	Yes.
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]	Soil	Half-life ≥ 182 days	Longest DT_{50}: 10.8 days (field dissipation study)	*Longest DT_{50}* **B-1**: 36.3 days **B-3**: 29.5 days **AB-1**: 0.02 days **B-2** and **AB-1 dimer**: Not available, but based on laboratory studies, they are not expected to persist in the environment.
	Water	Half-life ≥ 182 days	Longest DT_{50} in an aerobic water/sediment system (combined DT_{50}): 14.6 days Longest DT_{50} in an anaerobic water/sediment system (combined DT_{50}): 17.5 days	*Longest DT_{50} in water/sediment system (combined DT_{50})* **B-1**: 320 days (aerobic) **B-3**: Not available, but not expected to be found in water. **A-2**, **AB-1**, and **AB-1 dimer**: Not available, but based on laboratory studies, they are not expected to persist in the environment.
	Sediment	Half-life ≥ 365 days		

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Active Ingredient Endpoints**	**Transformation Products Endpoints**
	Air	Half-life ≥ 2 days or evidence of long range transport	Not found in volatile traps from biotransformation studies. Volatilisation is not expected to be an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<5.9 \times 10^{-6}$ Pa) and Henry's Law Constant ($<9.227 \times 10^{-7}$ atm·m^3/mol). The Applicant submitted a study on the calculation of Atkinson (PMRA# 2308948; not reviewed by the EAD). The calculated overall half-life for cyflumetofen degradation in air (reaction with OH radicals) was 12.7 hours.	**B-1** and **B-3**: Not available, but found in trace amounts in some volatile traps from aerobic biotransformation studies. **Others**: Not available
Bioaccumulation[4]	Log $K_{OW} \geq 5$		4.3	**Others**: Not required as a total residue BCF[5] value is available.
	BCF ≥ 5000		BCF value (L/kg): <250 (total residues)	The BCF value of <250 is based on the sum of all radiolabeled residues that would include **B-1**, **A-2**, **AB-1**, and **AB-1 dimer**. **B-3** is not expected to meet the criteria based on its high solubility and structure.
	bioaccumulation factor ≥ 5000		Not available	**All**: Not required as a total residue BCF value is available.
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, do not meet TSMP Track 1 criteria.

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] Field data (for example, bioaccumulation factors) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log K_{OW}).

[5] BCF = bioaccumulation factor

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 Differences Between Maximum Residue Limits in Canada and in Other Jurisdictions

Seven of the specified Canadian maximum residue limits (MRLs) are the same as those in the Unites States (U.S.). In four cases, the U.S. did not establish tolerances where Canada has established MRLs.

Table 1 Differences Between Canadian MRLs and in Other Jurisdictions

Commodity	Canada (ppm)	U.S. (ppm)	Codex* (ppm)
Apple sauce	0.6	None established	Not reviewed by Codex
Citrus peel	0.4	None established	
Milk	0.003	None established	
Fat, meat and meat byproducts of cattle, goats, horses, and sheep	0.03	None established	

* Codex is an international organization under the auspices of the United Nations that develops international food standards, including MRLs.

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. For animal commodities, differences in MRLs can be due to different livestock feed items and practices.

Under the North American Free Trade Agreement (NAFTA), Canada, the United States and Mexico are committed to resolving MRL discrepancies to the broadest extent possible. Harmonization will standardize the protection of human health across North America and promote the free trade of safe food products. Until harmonization is achieved, the Canadian MRLs specified in this document are necessary. The differences in MRLs outlined above are not expected to impact businesses negatively or adversely affect international competitiveness of Canadian firms or to negatively affect any regions of Canada.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number	Reference
2146667	2007, Identification of impurities in OK-5101 technical, DACO: 2.12.2,2.13.4,IIA 1.10.2 CBI
2146668	2007, Further validation of analytical method OTSA-0167 for OK-5101 and impurities, DACO: 2.12.2,2.13.1,2.13.2,2.13.4,IIA 1.10.2,IIA 2.5.2.1,IIA 2.5.2.4,IIA 4.2.1 CBI
2146669	2006, Physical properties: Nuclear magnetic resonance (NMR) of impurities of OK-5101 technical - A-2, B-2, AB-8, AB-9, AB-10, AB-11, AB-12, and AB-13, DACO: 2.12.2,2.13.2,2.13.4,IIA 1.10.2,IIA 2.5.2.3 CBI
2146670	2009, Composition of components in Cyflumetofen technical, DACO: 2.13.3,IIA 1.11.1 CBI
2146673	2004, Composition of components in OK-5101 technical (include validation of analytical methods), DACO: 2.13.1,2.13.3,7.2.5,IIA 1.11.1,IIA 1.11.2,IIA 4.2.1,IIA 4.2.7 CBI
2146674	2011, Cyflumetofen technical - Product identity and disclosure of ingredients, including manufacturing process, discussion of formation of impurities, and certified limits, DACO: 2.11.1,2.11.2,2.11.3,2.11.4,2.12.1,2.12.2,IIA 1.8.1,IIA 1.8.2,IIA 1.9.1.1,IIA 1.9.2,IIA 1.9.3
2146676	2002, OK-5101 pure: Determination of melting point, DACO: 2.14.4,IIA 2.1.1
2146677	2002, OK-5101 pure: Determination of boiling point, DACO: 2.14.5,IIA 2.1.2
2146678	2002, OK-5101 pure: Screening test for thermal stability, DACO: 2.14.13,IIA 2.1.3
2146685	2004, Determination of the flammability of OK-5101, DACO: 2.16,IIA 2.11.1
2146686	2004, Determination of the auto-ignition temperature of OK-5101, DACO: 2.16,IIA 2.11.2
2146687	2004, Statement on the explosive properties of OK-5101, DACO: 2.16,IIA 2.13
2146689	2004, Statement on the oxidizing properties of OK-5101, DACO: 2.16,IIA 2.15
2146693	2011, BAS 9210 I (TGAI): Determination of pH, DACO: 2.16,IIA 2.16
2146694	2011, Storage stability and corrosion characteristics of OK-5101, DACO: 2.14.14,IIA 2.17.1
2146697	2011, OK-5101: Stability to normal and elevated temperature, metals, and metal ions, DACO: 2.14.13,IIA 2.17.2
2146700	2003, OK-5101 pure: Determination of density, DACO: 2.14.6,IIA 2.2
2146702	2002, OK-5101 pure: Vapour pressure study, DACO: 2.14.9,IIA 2.3.1
2146703	2006, OK-5101 - Calculation of Henry's law constant, DACO: 2.16,IIA 2.3.2
2146705	2001, OK-5101 pure: Determination of color, DACO: 2.14.1,2.14.2,IIA 2.4.1
2146706	2001, OK-5101 pure: Determination of physical state, DACO: 2.14.1,2.14.2,IIA 2.4.1

PMRA Document Number	**Reference**
2146707	2006, Determination of appearance of OK-5101, DACO: 2.14.1,2.14.2,2.14.3,IIA 2.4.1,IIA 2.4.2
2146709	2001, OK-5101 pure: Determination of odor, DACO: 2.14.3,IIA 2.4.2
2146714	2002, OK-5101 pure: Determination of ultraviolet-visible absorption (UV/VIS) spectrum, DACO: 2.13.2,2.14.12,IIA 2.5.1.1,IIA 2.5.1.5
2146715	2002, OK-5101 pure: Determination of IR spectrum, DACO: 2.13.2,IIA 2.5.1.2
2146716	2006, Physical properties: Nuclear magnetic resonance (NMR), DACO: 2.13.2,IIA 2.5.1.3
2146717	2003, OK-5101 pure: Determination of mass spectrum, DACO: 2.13.2,IIA 2.5.1.4
2146718	2002, OK-5101 pure: Solubility study in water, DACO: 2.14.7,IIA 2.6
2146719	2003, OK-5101 pure: Solubility study in organic solvents, DACO: 2.14.8,IIA 2.7
2146720	2004, OK-5101 pure: Determination of n-octanol/water partition coefficient, DACO: 2.14.11,IIA 2.8.1
2146733	2006, OK-5101 - Calculation of dissociation constant, DACO: 2.14.10,8.2.3.2,IIA 2.9.5
2146736	2011, Multi-lateral submission for the evaluation of the active substance BAS 9210 I. OECD summary and evaluation (Tier II). Section 1: Identity, physical and chemical properties and further information, DACO: 10.6,12.7,2.16,8.6,Document M,IIA 3.10
2146737	2011, Sample of Analytical standards, DACO: 2.15,IIA 4.1.1
2146738	2004, OK-5101 technical: Determination of purity and stability, DACO: 2.13.1,7.2.5,IIA 4.2.1,IIA 4.2.7
2146739	2011, Evaluation of BAS 9210 I and its metabolite B-1 FDA multiresidue method (MRM) testing, DACO: 7.2.2,8.2.2.1,IIA 4.2.5,IIA 4.4
2146744	2007, Development and validation of an analytical method for the analysis of B-1 in soil, DACO: 8.2.2.1,IIA 4.4
2146745	2008, Development and validation of an analytical method for the analysis of AB-1 in soil, DACO: 8.2.2.1,IIA 4.4
2146747	2008, Development and validation of an analytical method for the analysis of 2-(trifluoromethyl)benzamide, B-3 in soil, DACO: 8.2.2.1,IIA 4.4
2146748	2011, Validation of BASF analytical method D1002: Determination of Cyfloumetofen (BAS 9210 I) and its metabolites in soil using LC-MS/MS, DACO: 8.2.2.1,IIA 4.4
2146749	2011, Independent laboratory validation of BASF analytical method D1002: Determination of Cyflumetofen (BAS 9210 I) and its metabolites in soil using LC-MS/MS, DACO: 8.2.2.1,IIA 4.4
2146750	2007, Development and validation of an analytical method for the determination of OK-5101 in soil, DACO: 8.2.2.1,IIA 4.4
2146751	2008, Development and validation of an analytical method for the analysis of 2-(trifluoromethyl)benzamide, B-3 in aqueous samples, DACO: 8.2.2.3,IIA 4.5

PMRA Document Number	Reference
2146752	2008, Development and validation of an analytical method for the analysis of AB-11 in iso-medium, DACO: 8.2.2.3,IIA 4.5
2146754	2009, Development and validation of an analytical method for the analysis of residues of B-1 in water, DACO: 8.2.2.3,IIA 4.5
2146755	2009, Development and validation of an analytical method for the analysis of residues of B-3 in water, DACO: 8.2.2.3,IIA 4.5
2146756	2007, Development and validation of an analytical method for the determination of OK-5101 residues in water, DACO: 8.2.2.3,IIA 4.5
2146758	2007, Development and validation of an analytical method for the analysis of AB-1 in 0.01 M CaCl2, DACO: 8.2.2.3,IIA 4.5
2146759	2007, Development and validation of an analytical method for the analysis of B-1 in 0.01 M CaCl2, DACO: 8.2.2.3,IIA 4.5
2146760	2009, Development and validation of an analytical method for the analysis of AB-1 in sediment, DACO: 8.2.2.2,IIA 4.6
2146762	2011, Validation of test solution preparations and analytical methods for use in the determination of BAS 9210-I in various media used in environmental toxicity studies (Including final report amendment), DACO: 8.2.2.2,IIA 4.6
2199457	2012, Summary and evaluation (Tier II & III) Document J, DACO: 0.8.11,0.8.12,Document J
2199458	2012, Composition of components in Cyflumetofen technical (Including amendment no. 2), DACO: 2.13.3,IIA 1.11.1 CBI
2199459	2012, Composition of components in Cyflumetofen technical (Including amendment no. 1), DACO: 2.13.3,IIA 1.11.1 CBI
2199460	2012, Composition of Components in OK-5101 Technical (Include Validation of Analytical Methods) (Including Amendment No. 1), DACO: 2.13.1,2.13.3,7.2.5,IIA 1.11.1,IIA 1.11.2,IIA 4.2.1,IIA 4.2.7 CBI
2199461	2012, Product Group A:Cyflumetofen Technical - Product Identity and Disclosure of Ingredients, Including Manufacturing Process, Discussion of Formation of Impurities, and Certified Limits, DACO: 2.11.2,IIA 1.8.2 CBI
2199462	2007, Determination of an active ingredient in OK-5101 pure grade (lot no.01E1), DACO: 2.13.1,IIA 4.2.1
2210997, 2210998	2012, Validation of test solution preparations and analytical methods for use in the determination of BAS 9210-I in various media used in environmental toxicity studies (Including final report amendment and final report amendment no. 2), DACO: 8.2.2.2,IIA 4.6
2355564	2013, Validation of method D1307: Determination of residues of Cyflumetofen (BAS 9210 I) metabolites, A-2, A-12 and AB-1 in surface and drinking water using LC-MS/MS, DACO: 8.2.2.3,IIA 4.5
2216376	2012, BASF Response to PMRA Clarification Notice for Cyflumetofen Technical, DACO: 2.12.2,2.13.4,IIA 1.10.2 CBI

PMRA Document Number	Reference
2216378	2012, Clarification Notice for Cyflumetofen Technical (2012-0156) dated 2012-07-18, DACO: 2.12.2,2.13.4,IIA 1.10.2 CBI
2145784	2011, Multi-lateral submission for the evaluation of the plant protection product BAS 9210 2 I. OECD summary and evaluation (Tier III). Section 1: Identity, physical and chemical properties and further information, DACO: 12.7,3.7,Document M
2145786	2011, Multi-lateral submission for the evaluation of the plant protection product BAS 9210 2 I. OECD summary and evaluation (Tier III). Section 2: Analytical methods, DACO: 12.7,3.7,5.1,7.1,8.1,Document M
2145799	2011, DACO 3.1.1 to 3.1.4, DACO: 2.1,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9,3.1.1,3.1.2,3.1.3,3.1.4,IIA 1.1,IIA 1.2,IIA 1.3,IIA 1.4,IIA 1.5.1,IIA 1.5.2,IIA 1.6,IIA 1.7
2145801	2011, BAS 9210 2 I: (Nealta miticide and Sultan miticide) - Group A - Product Identity, Composition and Analysis, DACO: 3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.3.2,3.5.4,IIIA 1.2.1,IIIA 1.2.2,IIIA 1.2.3,IIIA 1.3,IIIA 1.4.1,IIIA 1.4.2,IIIA 1.4.3.1,IIIA 1.4.3.2,IIIA 1.4.3.3,IIIA 1.4.4,IIIA 1.4.5.1,IIIA 1.4.5.2,IIIA 1.5
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2145855	2011, Validation of analytical method AFR0088/01: Determination of BAS 9210 I in BAS 9210 I SC formulations by reverse-phase HPLC Using UV Detection, DACO: 3.4.1,IIIA 5.2.1
2146655	2011, Multi-lateral submission for the evaluation of the active substance BAS 9210 I. OECD summary and evaluation (Tier II). Section 2: Analytical methods, DACO: 12.7,2.16,5.1,7.1,8.1 (OECD),Document M
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2146739	2011, Evaluation of BAS 9210 I and its metabolite B-1 FDA multiresidue method (MRM) testing, DACO: 7.2.2,8.2.2.1,IIA 4.2.5,IIA 4.4
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2145866	2011, BAS 9210 2 I - Acute dermal toxicity study in rats, DACO: 4.6.2,IIIA 7.1.2
2145868	2011, BAS 9210 2 I: Acute inhalation toxicity (nose only) study in the rat, DACO: 4.6.3,IIIA 7.1.3
2145870	2011, BAS 9210 2 I - Acute dermal irritation/corrosion in rabbits, DACO: 4.6.5,IIIA 7.1.4
2145871	2011, BAS 9210 2 I - Acute eye irritation in rabbits, DACO: 4.6.4,IIIA 7.1.5
2145876	2011, BAS 9210 2 I - Local lymph node assay (LLNA) in mice (CBA/CaCrl), DACO: 4.6.6,IIIA 7.1.6
2146768	2011, 14C-BAS 9210 I (Cyflumetofen) - Study on the plasmakinetics in mice (Including amendment no. 1), DACO: 4.5.9,IIA 5.1.1
2146769	2004, (14C)OK-5101 (Phenyl-ring-U- and Tolyl-ring-U-label): Metabolic fate in rats (preliminary study), DACO: 4.5.9,IIA 5.1.1
2146770	2004, (14C)OK-5101 (phenyl-ring-U-and tolyl-ring-U-label): Metabolic fate in rats (pharmacokinetics), DACO: 4.5.9,IIA 5.1.1
2146771	2004, (14C)OK-5101 (phenyl-ring-U-and tolyl-ring-U-label): Metabolic fate in rats (biliary excretion study), DACO: 4.5.9,IIA 5.1.1
2146773	2004, (14C)OK-5101 (phenyl-ring-U-and tolyl-ring-U-label): Metabolic fate in rats (quantitation and identification of metabolites in bile), DACO: 4.5.9,IIA 5.1.1
2146774	2004, (14C)OK-5101 (phenyl-ring-U-and tolyl-ring-U-label): Metabolic fate in rats (elimination balance), DACO: 4.5.9,IIA 5.1.1

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2146783	2003, OK-5101 - Acute dermal toxicity to the rat, DACO: 4.2.2,IIA 5.2.2
2146784	2003, OK-5101 - Acute (four-hour) inhalation study in rats, DACO: 4.2.3,IIA 5.2.3
2146785	2005, Acute inhalation study in rats with OK-5101: HLS study OSK 031/024380, DACO: 4.2.3,IIA 5.2.3
2146786	2003, OK-5101 - Skin irritation to the rabbit, DACO: 4.2.5,IIA 5.2.4
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2146788	2003, Assessment of contact hypersensitivity to OK-5101 in the albino guinea pig (maximisation-test), DACO: 4.2.6,IIA 5.2.6
2146791	2004, OK-5101: Repeated dose 28-day oral toxicity study in rats, DACO: 4.3.3,IIA 5.3.1
2146792	2004, OK-5101: Repeated dose 28-day oral toxicity study in rats, DACO: 4.3.3,IIA 5.3.1
2146793	2001, OK-5101: Repeated dose 2-week oral toxicity study in rats, DACO: 4.3.3,IIA 5.3.1
2146794	2003, 28-Day repeated oral dose toxicity study of OK-5101 in beagle dogs, DACO: 4.3.3,IIA 5.3.1
2146795	2003, 28-Day repeated oral dose toxicity study of OK-5101 in beagle dogs, DACO: 4.3.3,IIA 5.3.1
2146796	2004, OK-5101: Repeated dose 90-day oral toxicity study in rats, DACO: 4.3.1,IIA 5.3.2
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2146815	2007, Evaluation of DNA repair inducing ability of OK-5101 in male rat hepatocytes (in vivo rat hepatocyte DNA-repair assay), DACO: 4.5.8,IIA 5.4.5
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2351972	2013, BAS 9210 I (Cyflumetofen): Carcinogenicity study in rats, DACO: 4.4.2, 4.4.4,IIA 5.5.2
2383789	2013, Requested supplemental data from Cyflumetofen rat cancer studies, DACO: 4.4.2,4.4.4,IIA 5.5.2
2146823	2004, OK-5101: Carcinogenicity study in mice, DACO: 4.4.3,IIA 5.5.3
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2146827	2004, OK-5101: Reproductive toxicity study in rats, DACO: 4.5.1,IIA 5.6.1
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2146831	2003, Oral (stomach tube) developmental toxicity study of OK-5101 in rabbits, DACO: 4.5.2,IIA 5.6.10
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2146833	2008, Triethyltin bromide - Positive control study for neurotoxicity in Wistar rats single intraperitoneal administration, DACO: 4.5.12,IIA 5.7.1
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2146837	2008, Consultancy report - Toxicity prediction assessment of B-1, DACO: 4.8,IIA 5.8
2146838	2008, Consultancy report - Toxicity prediction assessment of B-3, DACO: 4.8,IIA 5.8
2146839	2009, Evaluation of DNA repair inducing ability of B-1 in male rat hepatocytes (in vivo rat hepatocyte DNA-repair assay), DACO: 4.8,IIA 5.8
2146840	2009, Evaluation of the mutagenic activity of 2-(trifluoromethyl)benzamide, B-3 in the Salmonella typhimurium reverse mutation assay and the Escherichia coli reverse mutation assay (with independent repeat), DACO: 4.8,IIA 5.8
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2146844	2004, Evaluation of the mutagenic activity of B-1 in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat), DACO: 4.8,IIA 5.8
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2199465	2012, Cyflumetofen - Oestrogen receptor binding assay using rat uterine cytosol, DACO: 4.5.8,IIA 5.4.5
2199466	2011, Cyflumetofen - H295R steroidogenesis assay, DACO: 4.5.8,IIA 5.4.5
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2210995	2012, Cyflumetofen - Oestrogen receptor binding assay using rat uterine cytosol, DACO: 4.5.8,IIA 5.4.5
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2213326	2004, Evaluation of the mutagenic activity of AB13 (impurity of OK-5101) in an in vitro mammalian cell gene mutation test with L5178Y mouse lymphoma cells (with independent repeat), DACO: 4.5.5,IIA 5.4.3
2266336	2012, BAS 9210 I (Cyflumetofen): Repeated dose 1-year oral toxicity study in rats, DACO: 4.3.2,IIA 5.3.4
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2146855	2011, Freezer storage stability of Cyflumetofen (BAS 9210 I) and its relevant metabolites in plant samples - Zero to twelve months analysis, DACO: 7.3,IIA 6.1.1
2146858	2004, Metabolic fate of (14C) OK-5101 (labeled in the phenyl and tolyl rings) in eggplants, DACO: 6.3,IIA 6.2.1
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2146865	2011, 14C-BAS 9210 I (Cyflumetofen) - Absorption, distribution and excretion after repeated oral administration in lactating goats, DACO: 6.2,IIA 6.2.3
2146869	2011, Magnitude of Cyflumetofen (BAS 9210 I) in Pomefruit Following Applications of BAS 9210 0I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.2
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2146874	2011, Magnitude of Cyflumetofen (BAS 9210 I) in strawberry following applications of BAS 9210 0I, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.4
2146875	2011, Raw agricultural commodity (RAC) residue evaluation of Cyflumetofen 20 SC applied to tomatoes, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.4
2146877	2011, Raw Agricultural Commodity Residue Evaluation Of Cyflumetofen 20 SC Applied To Grapes, DACO: 7.4.1,7.4.2,7.4.6,IIA 6.3.4
2146879	2011, Processed Commodity (PC) Residue Evaluation of Cyflumetofen 20 SC Applied to Tomatoes, DACO: 7.4.5,IIA 6.3.4,IIA 6.5.3
2146882	2011, Cyflumetofen: Justification to waive the data requirement for animal feeding study, DACO: 7.5,7.6,IIA 6.4.2
2146883	2011, Magnitude of Cyflumetofen residues in processed grapes following applications of Cyflumetofen, DACO: 7.4.5,IIA 6.5.3
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2145817	2004, Toxicity study in the parasitic wasp *Aphidius rhopalosiphi* with OK-5101 20 SC (laboratory test), DACO: 9.2.6,9.2.8,IIIA 10.5.1
2145819	2004, Dose response toxicity study in the predatory mite *Typhlodromus pyri* with OK-5101 20 SC (laboratory test), DACO: 9.2.6,9.2.8,IIIA 10.5.1
2145832	2006, Acute contact toxicity study in the honeybee with OK-5101 20% SC (laboratory test), DACO: 9.2.8,IIIA 10.6.2
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2146703	2006, OK-5101 - Calculation of Henry's law constant, DACO: 2.16,IIA 2.3.2
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2146731, 2146732	2004, (14C)OK-5101 (phenyl-ring-U-and tolyl-ring-U-label): A photolysis study in water, DACO: 8.2.3.3.2,IIA 2.9.2,IIA 7.6
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2146892, 2146893	2011, Anaerobic soil metabolism of 14C-BAS 9210 I, DACO: 8.2.3.4.4,IIA 7.1.2,IIA 7.2.4
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B. Additional Information Considered

Published Information

1.0 Environment

PMRA Document Number	**Reference**
2308948	Hayashi, N., et al, 2012, Cyflumetofen, a novel acaricide - its mode of action and selectivity, Pest Manag Sci (2013), 2012 Society of Chemical Industry, (wileyonlinelibrary.com) DOI 10.1002/ps.3470, DACO: 10.2.1

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PMRA Document Number	**Reference**
N/A	IRAC (Insecticide Resistance Action Committee) 2013. www.irac-online.org/eClassification accessed 10 May 2013